PHASE SOLUBILITY ANALYSIS IN STUDYING THE INTERACTION OF NIFEDIPINE WITH SELECTED CYCLODEXTRINS IN AQUEOUS SOLUTION

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ABSTRACT

The solubilizing potential and complexing tendencies of six cyclodextrins (CyD) with nifedipine in aqueous solution were evaluated using phase solubility methods. Solubility curves of nifedipine with β-CyD, 2-hydroxypropyl-β-CyD (2HP-β-CyD) and 2-hydroxypropyl-γ-cyclodextrin (2HP-γ-CyD) were classified as type A_L, while for heptakis (2,6-dimethyl)-β-CyD (DIMEB), randomly methylated-β-CyD (RAMEB) and γ-CyD, A_P type phase behaviour was observed. Stability constants, calculated from phase solubility diagrams, decreased in the order: DIMEB > RAMEB > β-CyD > 2HP-β-CyD > γ-CyD > 2HP-γ-CyD.

1. INTRODUCTION

Nifedipine (2,6-dimethyl-3,5-dicarboxyl-4-(2'-nitrophenyl)-1,4-dihydropyridine) is a calcium channel antagonist displaying very poor aqueous solubility and hence inferior dissolution and oral bioavailability. Recent studies have shown that the interaction of nifedipine with β-CyD,[1-3] 2HP-β-CyD[4] and some branched cyclodextrins[5,6] in aqueous solution and the solid state, have enhanced the above-mentioned physico-chemical properties. This study continues to investigate the solubilizing potential and complexing tendencies of γ-CyD, 2HP-γ-CyD, randomly methylated-β-CyD (RAMEB) and heptakis(2,6-di-O-methyl)-β-CyD (DIMEB) in aqueous solution using phase solubility techniques.

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2. MATERIALS AND METHODS

2.1. Materials

Nifedipine, β-CyD, γ-CyD, 2HP-β-CyD (Average Degree of Substitution, D.S. 4.8) and 2HP-γ-CyD (D.S. 5.3) were kindly donated by South African Druggists, Ltd (Port Elizabeth, South Africa). DIMEB and RAMEB (D.S. 12.4) were purchased from Cyclolab (Budapest, Hungary). Water for chromatography was obtained using a Milli-Q® water purification system (Waters Assoc., U.S.A.). All other materials were of analytical reagent grade.

2.2. Methods

Solubility measurements were carried out according to the method described by Higuchi and Connors.[7] Excess amounts of nifedipine were added to fixed volumes of 0.05M potassium phosphate buffer pH 5.8 containing various concentrations of CyDs. Nitrogen was passed through the preparations to avoid hydrolysis or photodegradation during equilibration. The solutions were shaken in a water-bath at 25°C ± 0.1°C for 24 hours, within which time equilibrium solubility of nifedipine was achieved. Each sample was centrifuged prior to analysis by HPLC. Phase solubility studies were performed in triplicate; from which apparent 1:1 and 1:2 stability constants (K)[7,8] were calculated. All phase solubility studies were performed in a dark-room under red light.

3. RESULTS AND DISCUSSION

Soluble substrate:ligand complexes were formed under the present experimental conditions with all CyDs studied (Figure 1). Nifedipine solubility increased linearly as a function of β-CyD, 2HP-β-CyD and 2HP-γ-CyD concentrations and thus the solubility curves were classified as type A_L,[7] indicating the formation of 1:1 substrate:ligand complexes. For DIMEB, RAMEB and γ-CyD positive deviations from linearity were observed at higher CyD concentrations, therefore displaying A_P-type[7] phase behaviour. This indicates the formation of higher order complexes, eg. 1:2 nifedipine : CyD, at high CyD concentrations in solution. The magnitude of the interactions between host and guest molecules, reflected by the stability constants (Table 1), decreased in the order DIMEB > RAMEB > β-CyD ≈ 2HP-β-CyD > γ-CyD ≥ 2HP-γ-CyD.

Generally, weak interactions were observed in solution between nifedipine and the CyDs, with only the highly hydrophobic derivatives, DIMEB and RAMEB, showing significantly high stability constants. The superior solubilizing potential of DIMEB and RAMEB has been frequently observed for many highly hydrophobic drugs.[9,10] The low aqueous solubility of β-CyD, and to a lessor extent γ-CyD, has been attributed to intramolecular hydrogen bonding between the secondary hydroxyl groups, thus imparting a rigidity to the

macrocycle and preventing hydration of Cyd by water. Selective or random methylation of β-CyD prevents the formation of these hydrogen bonds and consequently hydration of the CyD is made possible, therefore substantially increasing their solubility.[9,11] In addition, methylation of the hydroxyl groups expands the hydrophobic region of the CyD cavity, thus enhancing substrate binding via a hydrophobic effect.[12,13]

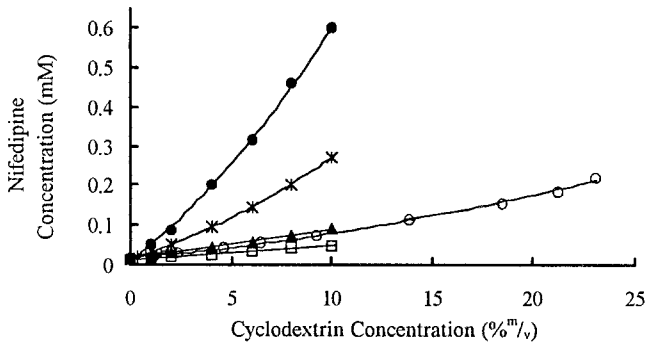

Figure 1. Phase solubility diagrams of nifedipine-cyclodextrin systems in 0.05M potassium phosphate buffer pH 5.8 at 25°C. Key: (●) DIMEB; (✱) RAMEB; (+) β-CyD; (▲) 2HP-β-CyD; (○) γ-CyD; (□) 2HP-γ-CyD.

The hydroxypropyl derivatives of γ- and β-CyD showed roughly equivalent or even slightly poorer solubilizing capacities when compared to their respective parent CyDs. This observation, however, is not uncommon and there are numerous drugs for which the solubilizing potential of these derivatives are reportedly similar or weaker than the parent CyDs.[10,14]

TABLE 1. Solubility enhancement (S.E.*), types of phase diagrams and stability constants (K) for nifedipine-cyclodextrin systems in 0.05M potassium phosphate buffer pH 5.8 at 25°C.

	Solubility enhancement	Type of diagram	Stability Constants (M^{-1})	
			$K_{1:1}$	$K_{1:2}$
β-CyD	2.1	A_L	77.9	–
γ-CyD	14.7	A_P	53.1	3.5
2HP-β-CyD	5.1	A_L	77.2	–
2HP-γ-CyD	3.3	A_L	49.3	–
RAMEB	19.5	A_P	184.9	5.8
DIMEB	37.5	A_P	283.1	11.3

* S.E.: Solubility enhancement in 10% $^m/_v$ aqueous solutions of respective cyclodextrin derivatives; in the case of β- and γ-CyD, maximum obtained solubility, namely 18.5 and 23.2 $\%^m/_v$, respectively.

4. CONCLUSION

Comparison of stability constants obtained from the phase solubility studies using β-CyD, γ-CyD, 2HP-β-CyD, 2HP-γ-Cyd, RAMEB and DIMEB indicates that the affinity of nifedipine is greater for the β-CyDs than for the γ-CyDs. It is proposed that the complex-forming moiety of nifedipine may be the 2'-nitrophenyl group; the dimensions of which would be more geometrically compatible for a closer and stronger interaction with the β-CyD cavity than for the larger γ-CyD cavity.

5. ACKNOWLEDGEMENTS

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