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Solubility Study of Nimodipine Inclusion Complexation with α- and β-Cyclodextrin and some Substituted Cyclodextrins

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Abstract

The solubility of nimodipine was measured in aqueous solutions of the following cyclodextrins: α-cyclodextrin (α-CD), hydroxypropyl-α-CD (HP-α-CD), β-cyclodextrin (β-CD), random substituted methyl-β-CD (M-β-CD), three hydroxypropyl-β-CDs (HP-β-CD) with mutually different average degree of substitution, and hydroxypropyl-γ-cyclodextrin (HP-γ-CD). From the determined linear solubility diagrams the values of the binding constant K_{11} of the inclusion complexes of nimodipine with the respective CDs were evaluated. The β-CDs efficiently solubilized sparingly soluble nimodipine, the highest value of K_{11} was found for M-β-CD (1680 M^{-1}), followed by β-CD (550 M^{-1}) and HP-β-CDs, where the higher degree of substitution lowered K_{11}. Only slight solubilization of nimodipine was observed in the solutions of the α-CDs and HP-γ-CD.

Introduction

The effectiveness of solubilization of a sparingly soluble hydrophobic compound in aqueous medium by means of its guest- host inclusion complexation with a cyclodextrin depends mainly on three factors: (i) The solubility of the inclusion complex formed, (ii) the solubility of the respective cyclodextrin, and (iii) the stoichiometry and the equilibrium binding constant of the complex formed in aqueous solution. In this work we determined values of the binding constant of the 1 : 1 complexes of the drug nimodipine with several cyclodextrins by measuring the solubility of the solid drug in aqueous cyclodextrin solutions. The dihydropyridine derivative nimodipine (Figure 1) is a calcium antagonist used in the treatment of cerebrovascular spasms [1, 2], and because of its poor aqueous solubility, the solubilization of this drug with the use of various cyclodextrins has been already under scrutiny [3–5].

In our recent studies, the peculiar course of nimodipine dissolution in aqueous solutions of some cyclodextrins, characterized by repeated episodes of supersaturation, was pointed out [4, 5]. Thus in the present work we followed the dissolution of solid nimodipine as a function of both cyclodextrin concentration and time, over the range of several days, to a couple of weeks, in order to determine reliable values of the corresponding equilibrium concentrations and the binding constant. Besides the parent cyclodextrins, α-CD and β-CD, the random substituted methyl derivative M-β-CD and several hydroxypropyl substituted derivatives, namely HP-α-CD, three HP-β-CDs with mutually different average degree of substitution, and HP-γ-CD were included in our study. We hoped such a selection of the commercially available chemically modified cyclodextrins would enable us to obtain more information, especially about the effect of hydroxypropyl substitution on the complexation ability of cyclodextrins, which is still a matter of interest and debate [6–9].

Experimental

Chemicals

α-Cyclodextrin (α-CD) and β-cyclodextrin (β-CD) were both purchased from Merck and Aldrich and no differences between the samples were found in this study. The substituted cyclodextrins were from Aldrich, they are characterized both by the average degree of substitution per one glucose unit and the average molecular weight, respectively written here in parentheses: hydroxypropyl-α-CD (HP-α-CD 0.6, 1180), methyl-β-CD (M-β-CD 1.8, 1310), three hydroxypropyl-β-CDs (HP-β-CD 0.6, 1380; 0.8, 1500; 1.0, 1540), and hydroxypropyl-γ-CD (HP-γ-CD 0.6, 1580). Unless given by the Aldrich catalogue, the approximate average molecular weight was calculated from the corresponding average degree of substitution per one glucose, the number of glucose units in the molecule of the cyclodextrin (α-CD 6, β-CD 7, γ-CD 8), and the formula molecular weight of the parent cyclodextrin (α-CD 972.9, β-CD 1135.0, γ-CD 1297.1). The parent γ-CD was not available for this work. The moisture content of the original cyclodextrins was determined by drying a small sample at low pressure at 110 °C

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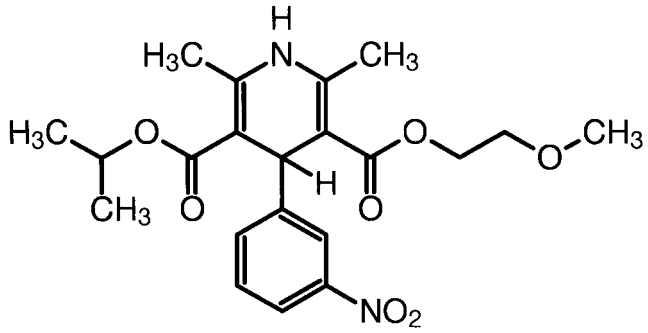

Figure 1. Nimodipine structure.

and proper corrections were made when aqueous solutions with required cyclodextrin concentration were prepared for the solubility measurements.

Nimodipine (nimotop, Figure 1) of chromatographic purity, yellowish powder, m.p. 125 °C, molecular weight 418.4, was obtained from the Research Institute of Drugs, Modra, Slovak Republic. Because of nimodipine's photolability, especially in solution [2], it must be kept in the dark or, for a short time, only dimmed light is allowed. This also applies rigorously for all manipulations with nimodipine solutions, especially during long term solubility measurements. When light protection is guaranteed, the nimodipine solutions are insensitive to degradation [2]. Deionized water was used in all the experiments and ethanol for UV spectrophotometry.

Equipment and the nimodipine solubility measurements

The suspension of an excess of finely powdered nimodipine, typically 100 mg in 100 mL of aqueous cyclodextrin solution (or in water), was stirred at ambient temperature 23–26 °C, for at least 4 days and in some cases even longer than 2 weeks, if necessary. At 1–2 day intervals (sometimes twice a day), small samples of the solution were repeatedly withdrawn, filtered through a G4 glass filter and ethanol was added to prevent nimodipine precipitation and to adjust the sample for the spectrophotometric determination. The nimodipine concentration was then determined via absorbance measurements in closed quartz cells with a Specord M40 (Carl Zeiss) spectrophotometer, at λ_{max} = 357–362 nm, larger shifts of λ_{max} were not observed in the solutions of various CDs. The calibration measurements were made in water–ethanol solutions of nimodipine and the respective cyclodextrin, the calibration curves were linear within experimental errors. By the described procedure, the time dissolution curves of nimodipine were measured at five to seven concentrations of each of the studied CDs in the range of 0.01–0.07 M, with the exception of the less soluble β-CD, where concentrations were 0.005–0.014 M. The use of ultrasound stirring was avoided since it may facilitate formation of non-equilibrium species in the solution.

Results and discussion

Solubility diagrams of nimodipine in the aqueous solutions of CDs

All the studied cyclodextrins more or less enhanced the poor aqueous solubility of nimodipine, thus proving a certain degree of its inclusion complexation in aqueous solutions. However, there were marked mutual differences between the CDs, with respect to both the solubilization efficiency and the time course of the nimodipine dissolution. The solutions of M-β-CD solubilized nimodipine most effectively, the measured time-dissolution curves were smooth and the equilibrium concentration of nimodipine was reached within 1–4 days at all the M-β-CD concentrations used. Although measured at the same conditions, the time-dissolution curves in the aqueous solutions of other CDs were different, usually less smooth and in some cases marked by irregular peaks of nimodipine concentration. Therefore especially in the solutions of weakly solubilizing α-CD, HP-α-CD, and HP-γ-CD, the long-term dissolution measurements with many repeated samplings were necessary for the evaluation of the reproducible nimodipine equilibrium concentrations. A one point determination may be misleading in solubility studies.

The evaluated equilibrium concentrations were plotted against the concentration of the respective CDs and in this way the phase solubility diagrams of nimodipine in the cyclodextrin solutions were constructed, as seen in Figure 2. In the case of M-β-CD, the corresponding line in Figure 2 represents only a small part of the actually measured range. However, in the entire measured concentration range of the studied CDs, all the nimodipine solubility diagrams were linear, of the type A_L after Higuchi [10]. The linearity is unequivocal in the solutions of M-β-CD and the three HP-β-CDs (r^2 = 0.995 or better), these cyclodextrins are well soluble and their solubilization effect is large. The parent β-CD exhibits a very good solubilization effect and a linear solubility diagram (r^2 = 0.993) but the accessible concentration range is narrow, because of the limited solubility of β-CD itself (Figure 2). In the solutions of the well soluble α-CD, HP-α-CD, and HP-γ-CD, the linearity of the solubility diagrams is less pronounced (r^2 = 0.91–0.97), due to their small solubilization effect. The diagrams do not indicate eventual formation of poorly soluble nimodipine–CD complexes.

Binding constant of the nimodipine inclusion complexes with CDs

With regard to the linear solubility diagrams, the formation of the 1 : 1 nimodipine–CD complexes [10, 11] was assumed in the aqueous solutions of all the studied cyclodextrins. The respective values of the equilibrium binding constant K_{11} (the apparent stability constant) of the complexes were calculated from a known equation [3, 10, 11], modified as follows:

$$K_{11} = \frac{a}{c_{0N}(1-a)}.$$

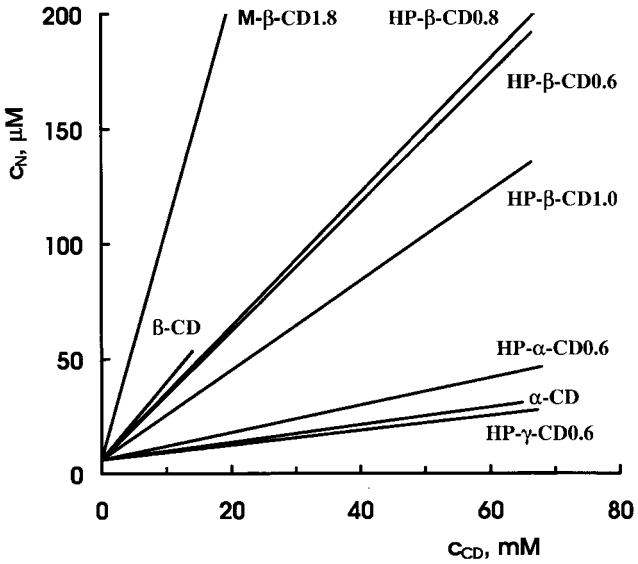

Figure 2. Solubility diagrams of nimodipine in the solutions of the studied cyclodextrins, c_N (μM) and c_{CD} (mM) are the respective concentrations of nimodipine and the cyclodextrin; the numerals after the CD symbols are the respective degrees of substitution.

Table 1. Binding constant K_{11} of the inclusion complexes of some cyclodextrins with nimodipine

Cyclodextrin	Degree of substitution	K_{11} (M^{-1})
α-CD	–	62 ± 14
HP-α-CD	0.6	97 ± 10
β-CD	–	550 ± 32
M-β-CD	1.8	1680 ± 70
HP-β-CD	0.6	460 ± 43
HP-β-CD	0.8	480 ± 25
HP-β-CD	1.0	320 ± 13
HP-γ-CD	0.6	52 ± 15

Coefficient $a = \Delta c_N/\Delta c_{CD}$ is the slope of the solubility diagram of nimodipine (c_N) in the aqueous solution of the respective cyclodextrin (c_{CD}), obtained by the least squares method, and c_{0N} is the aqueous solubility (intrinsic solubility) of nimodipine. The correct value of c_{0N} is another critically important factor for reliable calculations of mutually consistent values of the binding constant, therefore we used the carefully measured nimodipine solubility in water, $c_{0N} = 6.1 \times 10^{-6}$ M, not an intercept obtained from the least squares analysis. The values obtained for the binding constant K_{11} are listed in Table 1.

The binding constant determined in this work must be regarded as a kind of macroconstant, since the studied substituted CDs are in fact mixtures of related isomers and each of the parent α-CD and β-CD may also bind the rather complicated nimodipine molecule by more than one mode. Our K_{11} of the nimodipine complex with β-CD (550 M^{-1}) is however in reasonable agreement with the result of Japanese authors (480 M^{-1} [3]). The methyl substitution in M-β-CD greatly enhances both the cyclodextrin solubility and its complexation ability, expressed by the highest value of K_{11} in Table 1. On the other hand, our results for the three well soluble HP-β-CDs show that the hydroxypropyl substituent, especially at the higher degree of substitution, diminishes the complexation ability towards nimodipine in comparison with the parent β-CD which is in disagreement with the mentioned older work [3]. However, some recent studies of other complexes of HP-β-CDs [8, 9] point out that although the hydroxypropyl group often facilitates formation of inclusion complexes, in some cases it may hinder the penetration of a bulky guest molecule into the otherwise optimal β-CD cavity. The steric hindrance is more probable at higher degree of substitution, in agreement with our findings.

The complexation ability of α-CD, HP-α-CD and HP-γ-CD towards nimodipine is much weaker than that of the discussed β-CDs. Values of K_{11} for α-CD and HP-α-CD in Table 1 are in the range found for the complexes of α-CD with small organic molecules like esters [12], suggesting that one of the ester side chains of nimodipine (Figure 1) may be involved in rather superficial complexation by the smaller cavity of α-CDs. Such complexation of the polar side chain may be facilitated by the hydrophilic hydroxypropyl group, which is indeed reflected by the somewhat higher K_{11} of HP-α-CD in comparison with α-CD. On the other hand, the lowest K_{11} of HP-γ-CD apparently indicates that the size of the cavity of this higher cyclodextrin is too large for effective nimodipine complexation.

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