Cyclodextrine vs D-glucose in the Solutions of the Derivative of 1,4-DHP

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Abstract

Hydrophilic and hydrophobic cyclodextrins (CDs) have found a lot of applications in medicine pharmacology, food processing and cosmetology. They can function as a drug carrier material and parent host molecules, increasing drug biocompatibility, optimizing the efficiency of drug activity, and controlling drug release at the desired level. The effectiveness of CD complexation depends on many factors such as the type and the size of both the CD molecule itself and the guest molecule, pH of the solution, and temperature. In aqueous solution of glucose the aggregation of molecules can occur leading to the formation of CD-like structures. In the paper the possibility of the formation of the inclusion complexes of CD and glucose with Nimodipine was investigated with the aid of ultrasonic spectroscopy. By comparing the efficiency of industrial saccharides and glucose in the formation of the inclusion complexes the cost effectiveness of the use of glucose as a substitute for CD can be determined.

Keywords: Cyclodextrin, α-D-glucose, Nimodipine, ultrasounds, host-guest complexes

1. Introduction

The interest in the multicomponents systems has possibly influenced the multidisciplinary approach to the study of supramolecular compounds as well as stimulated their practical applications. To optimise the efficacy of drug activity and control its release, some drug carrier materials, such as cyclodextrins (CDs) have been designed. CDs are small cyclic maltoologisaccharides with six to nine glucose residues. They haves the shape of torus-like macro ring. It is generally accepted that in aqueous solutions CDs form "inclusion complexes" where water molecules located in the central cavity are replaced by a lipophilic guest molecule. CDs can form complexes with chemical compounds of appropriate size. If the guest is the wrong size, it will not fit properly into the cyclodextrin cavity and some of his functional groups will not penetrating the cavity. The CDs complexes are relatively stable, however, they show poor water solubility (in comparison with simple sugars) and precipitate easily from the solution as crystal form.

CDs are often modified by exchanging the outer hydrogen atoms in hydroxyl groups with the ones that bond with oxygen. In this way the cyclodextrine derivatives such as β-cyclodextrin and methyl-β-cyclodextrin (MBCD) can be produced which have better

solubility in aqueous solution (several dozen times). The MBCD was used in the present study [1-3].

α-D-glucose also known as dextrose belongs to the class of organic compounds known as hexoses and is the end product of photosynthesis. The cyclic form which is present in highest concentrations in aqueous solutions arises from the open-chain form by an addition reaction between the aldehyde group and hydroxyl group. Moreover, glucose molecules in aqueous solutions undergo the process called mutarotation. The ring then unfolds back to the open chain form with inverse location of groups at the first carbon atom. The process takes place as long as necessary to reach equilibrium in the solution.

Nimodipine (NM) is a 1,4-dihydropyridine derivative calcium ion channel blocker, applying to improve the blood circulation in the acute cerebrovascular disease. Administered by oral tablets Nimodipine has the low bioavailability, about 13%. Furthermore, the drug is water-insoluble but is soluble in alcohol and decomposes easily under the light. The bioavailability, water-solubility and light stability of Nimodipine could be enhanced by the inclusion of cyclodextrin [4, 5].

In this paper the possibility of the formation of inclusion complexes of MBCD or α-D-glucose with Nimodipine was investigated with the aid of ultrasonic spectroscopy. The efficiency of complex formation in both solutions is also determined.

2. Materials and Methods

The following chemicals were used in this work: Nimodipine (98% purity) was obtained from Sigma Aldrich, ethanol (purity of 99.9%) from POCH, metylo-β-CD (purity > 98%) from Wacker Chemie GMBH, and α-D-glucose (purity > 98%) from Sigma Aldrich. All chemicals were used without further purification. The solutions were prepared with double-distilled and deionized water. First, the standard solutions were prepared but due to the poor solubility of Nimodipine in water it was decided to use aqueous-alcoholic solvent as an environment for the formation of inclusion complexes. Nimodipine is well soluble in ethanol. If the water were to be the only solvent, the preparation of the solutions of appropriate sugar and Nimodipine would require very low concentrations of the drug. But then because of the small volume of the ultrasonic measuring cell (0.7 mL) the measurement error would be very high. For this reason the initial solutions were prepared as binary and, after the solubility analysis, it was decided that the ratio of their components (α-D-glucose or MBCD to water and NM to ethanol) of 1:750 for each sample is sufficient for carrying out the reliable acoustic measurements and does not lead to the saturation of the solution.

The volume of the sample was 5 mL and the volumes of the solvents were calculated from the expression:

$$V_t = \frac{1 - x_2}{c_1} + \frac{x_2}{c_2} \tag{1}$$

where x_2 is the molar concentration of Nimodipine; c_1 and c_2 are the molarities of the solutions: water with sugars and ethanol with the drug, respectively. It should be noted that for each solution the volumes of the components within the concentrations range of

0–1 mole fraction of Nimodipine are normalized and they sum to 5 mL. The 29 samples for acoustic measurements were prepared according to the procedure described above. Because of the difference in molar mass between MBCD and α-D-glucose, the amount of α-D-glucose in solution was seven times bigger than the amount of MBCD thereby it can be assumed that the sugar contents in both solutions were comparable.

The ultrasonic method was used which makes possible to study elastic properties of liquids and thereby their change in rigidity in order to check whether the cavitants are formed in the studied system of sugar (MBCD or α-D-glucose) + NM. From the speed of sound, c, and the density, ρ, the isentropic compressibility can be calculated from the Laplace equation $k_S = 1/\rho c^2$. Isentropic compressibility can be transformed into its molar counterpart via the relation $K_{S,m} = V_m k_S$, where V_m is the molar volume. The efficiency of the formation of supramolecular complexes can be determined from the excess molar isentropic compressibility, $K_{S,m}^E$, that is the difference between molar isentropic compressibility of the studied mixture calculated from Laplace equation and the molar compressibility for the ideal mixture obeying the Raoult law:

$$K_{S,m}^E = K_{S,m} - K_{S,m}^{id} \tag{2}$$

Since the ideal isentropic compressibility does not obey so-called ideal mixing law, it must be evaluated from the well know thermodynamic identity [6]:

$$K_{S,m}^{id} = \sum_i x_i \left\{ K_{S,i}^* - T \cdot A_{p,i}^* \left[\left(\sum_i x_i A_{p,i}^* \Big/ \sum_i x_i C_{p,i}^* \right) - \left(A_{p,i}^* / C_{p,i}^* \right) \right] \right\} \tag{3}$$

where $A_{p,i}^*$ is the product of the molar volume $V_{m,i}$ and the isobaric expansivity $\alpha_{p,i}^*$, $C_{p,i}^*$ is the isobaric molar heat capacity, $K_{S,i}^*$ is the product of the molar volume V_i and the isentropic compressibility $k_{S,i}^*$ referred to "pure" i-th liquid component. In our case the "pure" components are the initial solutions, e. g. for $x_2 = 0$ and $x_2 = 1$. This principle was also applied to the evaluation of excess molar volume, V_m^E, using molar masses M_{x_1}, M_{x_2} and densities, ρ_{x_1}, ρ_{x_2}, of the components

$$V_m^E = \frac{M}{\rho} - \left[(1 - x_2) \frac{M_{x_1}}{\rho_{x_1}} + x_2 \frac{M_{x_2}}{\rho_{x_2}} \right] \tag{4}$$

The measurements of ultrasound velocity and density were carried out in the temperature range of 288.15–313.15 K. Molar heat capacity was also measured since its value is necessary to calculate ideal isentropic compressibility from Eq. (3).

Speed of ultrasonic wave was measured by a resonance method using the ResoScan™System (Germany) apparatus. The ultrasonic speed is determined from the change in resonance frequencies which arise when the ultrasonic signal is transmitted through the path length of the measurement cell. The change in resonance frequencies occur when ultrasonic wave frequency is tuned within a range of 7.3–8.4 MHz. The system permits the measurements of the ultrasonic velocity with the accuracy of ±0.01 m/s with temperature precision of ±0.01°C. The density was measured using a microprocessor gauge of the DMA 38 type by Anton Paar. This instrument permits

density measurements up to 3×10^3 kg/m^3 with an accuracy of ± 0.2 kg/m^3. The isobaric molar heat capacity was measured by using DSC Q2000 (TA Instruments) with temperature accuracy of ±0.01 K. The heating rate was 2 K/min. Each sample was heated from 270 K to 330 K.

3. Results and discussion

The results of the velocity measurements for MBCD + NM and α-D-glucose + NM systems as a function of the concentration of Nimodipine (in mole fraction) are shown in Figures 1a and 1b.

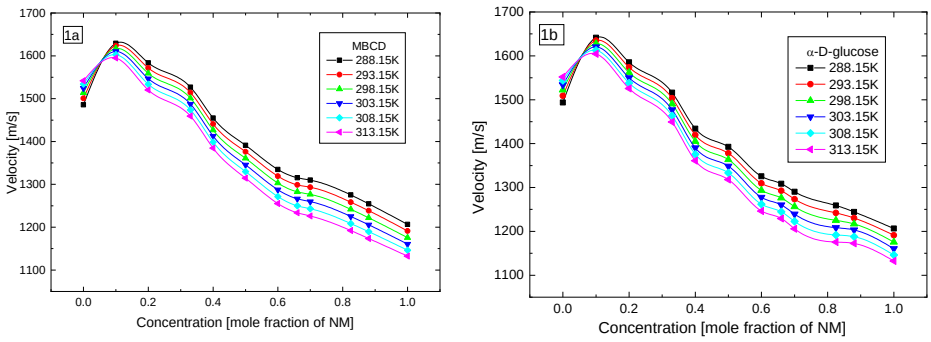

Figure 1. Ultrasound velocity as function of Nimodipine concentration:
a) in the system of MBCD + Nimodipine, b) α-D-gluocse + Nimodipine

For both systems the velocity isotherms shown in Figures 1a and 1b intersect and then reach their maxima at the concentration of 0.1 mole fraction of Nimodipine which is due to the introduction of the ethanol to the system (clathrates formation in ethanol-water mixture). The value of the ultrasound velocity at maximum depends on temperature. For higher concentrations of Nimodipine the ultrasound velocity decreases monotonically.

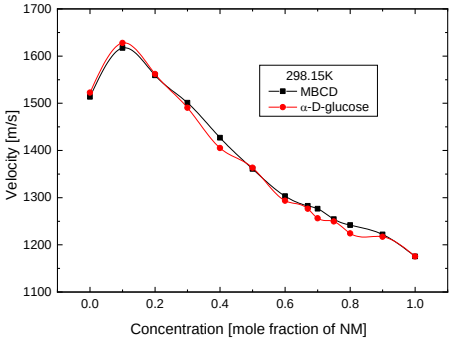

Figure 2. Ultrasound velocity vs Nimodipine concentration at the temperature of 298.15 K in the systems of MBCD + NM and α-D-glucose + NM

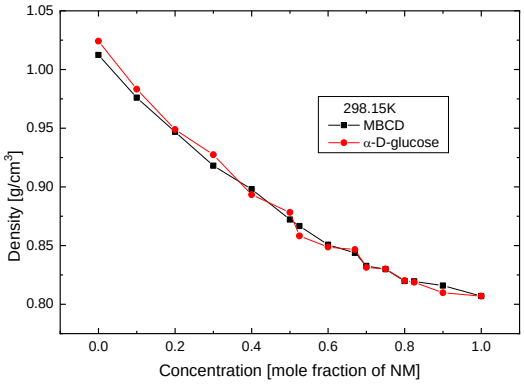

Figure 3. Density vs Nimodipine concentration at the temperature of 298.15 K in the systems of MBCD + NM and α-D-glucose + NM

Figure 2 shows the dependence of ultrasound velocity and Figure 3 the dependence of density on the concentration of Nimodipine in both systems, with MBCD and α-D-glucose, at the same temperature of 298.15 K. The greatest difference in ultrasound velocities in both systems amount to only 21.8 m/s, so it can be said that it is not velocity alone that can affect the efficiency of complexation process of one sugar or the other with Nimodipine.

The results of the measurements of molar heat capacity necessary for the evaluation of the excess molar isentropic compressibility are shown in Figure 4.

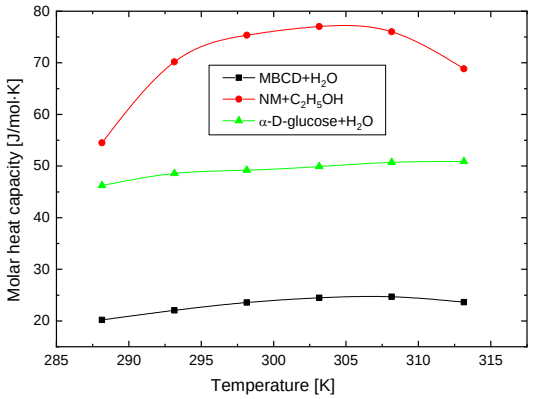

Figure 4. Molar heat capacities for the initial solutions

It should be noted that while density and velocity results were close to each other for both systems, their molar heat capacities differ significantly. It is related to the difference in the structure between MBCD and α-D-glucose. Although glucose imitate cyclodextrin, mutaroration does not lead to the formation of equally strong glycosides bonds as in CDs.

The excess molar isentropic compressibilities plotted against mole fraction of Nimodipine (presented in Figure 5) show the influence of the reactions taking place in the studied solutions on the final structure of the complexes that are formed in sugar/drug solutions.

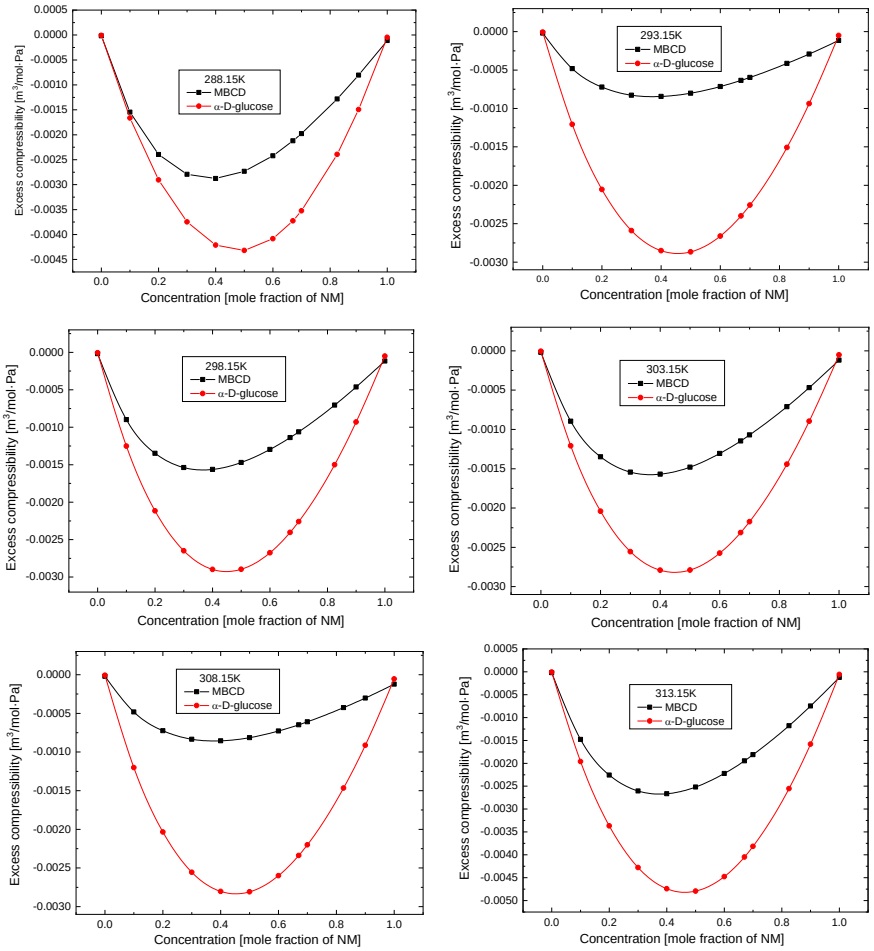

Figure 5. Excess molar compressibility, $K_{S,m}^{E}$, for MBCD + Nimodipine and D-glucose + Nimodipine plotted against mole fraction of Nimodipine at various temperatures: 288.15, 293.15, 298.15, 303.15, 308.15, and 313.15 K to 313.15 K

For initial solutions the molar isentropic compressibility of the real mixture is of course equal to that of ideal mixture so the excess compressibility has the value of zero. With the addition of the drug the excess molar compressibility for both solutions takes the negative values for the entire composition ranges and all temperatures. The shift

from ideality is in the direction of the enhanced rigidity. The minimum of excess molar compressibility occur at 0.5 mole fraction of Nimodipine indicating that the compound formed is composed of one molecule of the host (sugar) and one molecule of the guest (drug).

The analysis of the temperature dependence of excess molar compressibility shown in Figure 5 reveals that both solutions (cyclodextrin + Nimodipine and α-D-glucose + Nimodipine) reach their minimum values at the lowest (288.15 K) and the highest (313.15 K) temperatures. Thus regardless of host molecule these outermost temperatures make the best conditions for the complexation process inside both polysaccharides but in favor of the 288.15 K because too high temperature may destabilize the properties of the drug. It also worth noting that the values of the excess molar isentropic compressibility are lower for the solution with α-D-glucose than that with MBCD for all the studied temperatures. It may point out to the more frequent complex formation in the systems with glucose, independently on external conditions.

To determine the efficiency of complexation process through the amount/dose of drug encapsulated in the complex, in possibly better absorbed form, the masses of the sugar (MBCD or α-D-glucose) and the drug (Nimodipine) in the solutions have to be calculated. The results of the calculation are presented in Table 1.

Table 1. Masses of the components of the solutions for the samples studied; m_1 is the mass of sugar (MBCD or α-D-glucose) and m_2 the mass of NM

Solution studied	Temperature [K]	m_1 [mg]	m_2 [mg]
MBCD + NM	288.15	143.77	31.60
	293.15	149.96	30.90
	298.15	151.23	30.76
	303.15	150.39	30.85
	308.15	148.28	31.09
	313.15	147.04	31.23
α-D-Glucose + NM	288.15	116.71	35.82
	293.15	125.72	34.78
	298.15	128.34	34.62
	303.15	128.71	34.58
	308.15	127.21	34.74
	313.15	122.79	35.19

To achieve comparable efficiency in the same temperature the complex of MBCD + Nimodipine require more sugar and the complex of α-D-glucose + Nimodipine – more drug. However, it should be remembered that MBCD has the structure designed for complexation while glucose is very reactive as chemical. So the lower values of the excess molar compressibility for the solution of Nimodipine with α-D-glucose can be attributed to other processes taking place in this solution apart from complexation. But even that does not indicate that MBCD is a better candidate for the host molecule than α-D-glucose and both sugars are comparable in terms of formation inclusion compounds.

4. Conclusions

The ultrasonic and volumetric investigations of the systems MBCD + Nimodipine and α-D-glucose + Nimodipine lead to the following conclusions on the complexation processes in the solutions: (1) The properties of the components of the solutions have direct influence for the complexation process; (2) It was found that both sugars (MBCD and α-D-glucose) are able to form complexes with Nimodipine; (3) The values of the excess molar isentropic compressibility are negative for the entire composition ranges and all temperatures regardless the type of sugar used in the solution what suggests that formed structure is packed, relatively rigid and reaches the energetic balance for the stechiometric ratio of 1:1.

The better knowledge about the inclusion complexation processes and their dynamics in the such specific systems as sugars and a 1.4-dihydropyridine derivative will make possible for them to find more applications in medicine.

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