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Research paper

The solubilization of the poorly water soluble drug nifedipine by water soluble 4-sulphonic calix[*n*]arenes

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Abstract

In this study, the solubilizing effect of 4-sulphonic calix[*n*]arenes on the poorly water soluble drug nifedipine was investigated. 4-Sulphonic calix[*n*]arenes are water-soluble phenolic cyclooligomers that form complexes with neutral molecules such as nifedipine. Solubility experiments were performed at 30 °C using the Higuchi rotating bottle method. The amount of nifedipine in solution was determined by HPLC. The results showed that the size of the 4-sulphonic calix[*n*]arenes, the pH of solubility medium, and the concentration of the calix[*n*]arenes all significantly changed the solubility of nifedipine. 4-Sulphonic calix[8]arene improved the solubility of nifedipine the most, about 3 times the control at 0.008 M and pH 5, followed by 4-sulphonic calix[4]arene, about 1.5 times the control at 0.008 M and pH 5, while in the presence of 4-sulphonic calix[6]arene, the solubility of nifedipine was decreased. The possible mechanisms involving in the complexation between 4-sulphonic calix[4]arenes, 4-sulphonic calix[8]arene and nifedipine may be a combination of hydrogen bonding, hydrophobic bonding, and possibly electron donor–acceptor interactions. However, the degree to which these forces promote the formation of nifedipine:4-sulphonic calix[*n*]arene complexes with increased solubility was limited by conformational changes in the 4-sulphonic calix[*n*]arene molecules.

Keywords: Nifedipine; Solubilization; 4-Sulphonic calix[*n*]arenes

1. Introduction

The 1,4-dihydropyridine L-type calcium-channel blocker nifedipine, Fig. 1, is an important calcium channel blocker that is used extensively for the clinical management of a number of cardiovascular diseases such as essential hypertension, congestive heart failure, and cerebral ischemia [1]. A major pharmaceutical problem associated with nifedipine is its poor aqueous solubility, 5–6 μg/ml over a pH range of 2–10, which may account for its highly variable bioavailability in humans [1,2]. Among the various techniques employed to enhance the dissolution and/or aqueous solubility of nifedipine, drug-excipient complexes with increased solubility have been reported for the following complexing agents: salicylates [3], phenolic ligands [1], nicotinamide [4], β-cyclodextrin and hydroxypropyl β-cyclodextrin [5–7].

Since cyclodextrins are able to encapsulate nifedipine into their hydrophobic cavity [5–7], other supramolecular host compounds might also form host–guest complexes with nifedipine. Along with the cyclodextrins and crown ethers, calixarenes are the third major class of supramolecular host systems [8,9]. The calixarenes, Fig. 1, are a class of cyclooligomers formed via a phenol–formaldehyde condensation. They exist in a 'cup' like shape with a defined upper and lower rim and a central annulus. Their rigid conformation enables calixarenes to act as host molecules because of their preformed hydrophobic cavities. Due to this ability to form host–guest type complexes with a variety of organic or inorganic compounds the calixarenes have received increasing attention during the last two decades [8–10]. In addition, the ease with which various functional groups can be introduced to either the upper or the lower rim of the 'cup', makes it easy to change the affinity of these cyclooligomers towards target molecules

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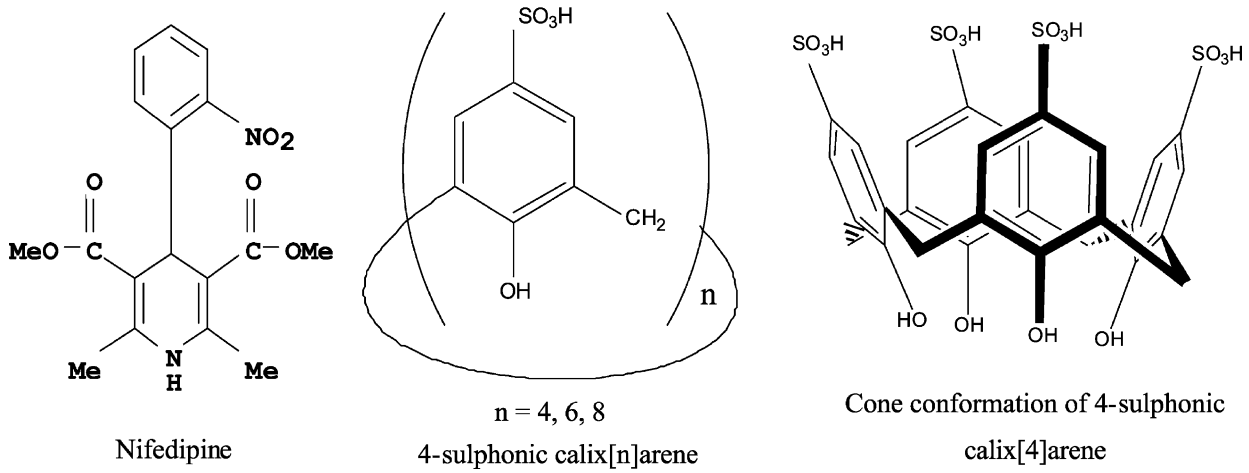

Nifedipine

n = 4, 6, 8

4-sulphonic calix[n]arene

Cone conformation of 4-sulphonic calix[4]arene

Fig. 1. Molecular structures of nifedipine and the 4-sulphonic calix[*n*]arenes.

and/or increase the solubility of the calixarenes [11–13]. One such modified calixarene, the water-soluble 4-sulphonic calix[*n*]arenes may selectively include various guests according to their size and hydrophobicity in a manner similar to cyclodextrins [14–16]. Although the calixarenes are currently not approved by the FDA for use in medicines to date the calixarenes have demonstrated neither toxicity nor immune responses [9]. This further increases interest their use in the field of biopharmaceutical applications beyond their current use for the chiral separation of molecules [11], as carriers of marker molecules in novel analytical techniques [22] and as complex forming agents to remove molecules from the environment [26].

To date only one report about the effect of the water-soluble 4-sulphonic calix[*n*]arenes on the solubility of drugs has been reported [17]. This study showed that depending on the size of the calixarene and the pH of the solution, the sulphonated calixarenes significantly increased the aqueous solubility of the water insoluble drug testosterone. The aim of the present study was to determine the effect of 4-sulphonic calix[*n*]arenes on the solubility behavior of nifedipine. Three sulphonated calixarenes with increasing number of phenolic units in the ring, the pH of the aqueous solubility medium, and the concentration of calix[*n*]arene were changed to gain a better understanding of the solubilizing effect of 4-sulphonic calix[*n*]arene had on nifedipine.

2. Materials and methods

2.1. Materials

Nifedipine (Fig. 1, $C_{17}H_{18}N_2O_6$, MW = 346) was purchased from Sigma Chemical Company (St Louis, MO, USA). 4-Sulphonic calix[4]arene hydrate ($C_{28}H_{24}O_{16}S_4{\cdot}9H_2O$), 4-sulphonic calix[6]arene hydrate ($C_{42}H_{36}O_{24}S_6{\cdot}13H_2O$), 4-sulphonic calix[8]arene hydrate ($C_{56}H_{48}O_{32}S_8{\cdot}21H_2O$) were purchased from Acros Organics (Geel, Belgium). The molecular structures of the calix[*n*]arenes are given in Fig. 1. Methanol used for chromatographic assay of nifedipine was of HPLC grade (Spectrum Chemical Company, Gardena, CA). For both the solubility studies and HPLC analysis deionized water was used (Nanopure, Barnstead International, Dubuque, Iowa). All the other chemicals and solvents were of analytical reagent grade and used as received.

2.2. Water determination

Thermogravimetric (TG) analysis, Fig. 2, was performed on the calix[*n*]arenes to determine the amount of crystalline water contained in the crystal structures. TGA traces were measured with a Hi-Res Modulated TGA 2950 (TA Instruments, New Castle, DE). Samples weighing approximately 5 mg were heated at 20 °C min^{-1} under nitrogen gas flow of 35 ml min^{-1}. In addition to TG analysis the moisture content was also determined with a Mettler DL18 Karl Fischer titrator (Mettler-Toledo, Inc., Columbus, OH). The Karl Fischer solution was calibrated against a predetermined mass of water. About 15 mg of

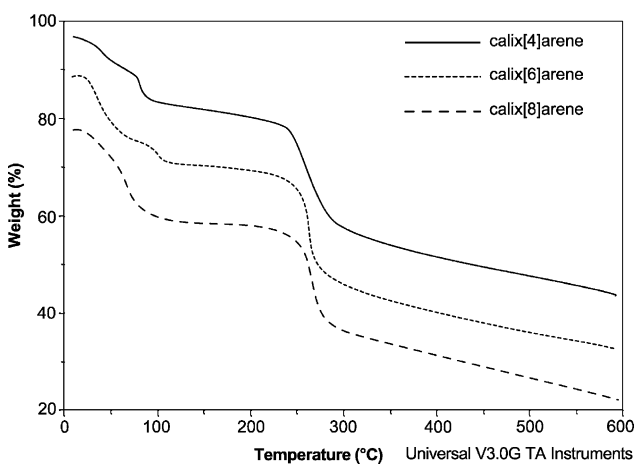

Fig. 2. TGA curves of the 4-sulphonic calix[*n*]arenes.

powder was accurately weighed and added to the methanol, previously neutralized with the Karl Fischer solution, in the titration beaker. The mixture was stirred magnetically and titrated with the Karl Fischer solution. The experiment was done in duplicate and the percentage water (w/w) calculated.

2.3. HPLC analysis of nifedipine

Both nifedipine and calixarenes have strong UV absorption, so HPLC method was developed to determine the concentration of nifedipine in the solution. The HPLC method used in this study complied with specifications for precision, accuracy, selectivity, linearity, and ruggedness as required by the USP XXIV [18]. Analysis was carried out with an automated high performance liquid chromatograph (AS1000 autosampler and P2000 pump, Thermo Separation Products, Waltham, MA) with a UV detector (UV3000 detector) set at 254 nm. Nifedipine eluted on a Econosil C_{18} column (250 × 4.6 mm, 5 μm, Alltech, Deerfield, Il) after 11 min, whereas 4-sulphonic calix[*n*]arenes eluted at approximately 2.5 min using a mobile phase of water: methanol (2:1 v/v) (Fig. 3); flow rate 0.7 ml min^{-1}; injection volume 20 μl. The solutions were prepared in the dark to prevent nifedipine photodegradation. Each determination was conducted triplicate.

2.4. Solubility measurements

The solubility of nifedipine in TRIS buffers composed of varying concentrations of citric acid, potassium dibasic phosphate, sodium tetraborate and tris((hydroxymethyl)-aminomethane) to obtain solutions with pH 5, 7 or 12 was determined at 30 °C and increasing concentrations of the 4-sulphonic calix[*n*]arenes. The Higuchi rotating bottle method for solubility determination by adding an excess of nifedipine powder to screw-capped amber vials (three replicates) containing 3 ml buffer solution and increasing amounts of the 4-sulphonic calix[*n*]arenes [19]. For each set of experimental conditions three vials were rotated at 60 rpm at 30 °C until no further increase in the solubility of nifedipine was observed. The solutions were passed through 0.45 μm cellulose acetate filters (Osmonics Inc., Minnetonka, MN), the filtered liquids collected and the concentration of nifedipine in solution determined by HPLC.

Phase solubility diagrams were constructed by plotting the molar concentration of nifedipine dissolved (solubility) versus molar concentration of calix[*n*]arenes. From these diagrams, the stability constants for the complexation of nifedipine with calix[*n*]arenes were calculated as described by Higuchi and Connors [19].

2.5. Statistical analysis

Solubility results obtained from experiments were evaluated using a SAS, SAS Institute Inc., Cary, NC. A *P*-value of <0.05 was considered statistically significant.

3. Results

Some important physicochemical properties of the three water-soluble 4-sulphonic calix[*n*]arenes with $n = 4$, 6 and 8 repeating phenolic units (Fig. 1) are given in Table 1. 4-Sulphonic calix[4]arene, 4-sulphonic calix[6]arene and 4-sulphonic calix[8]arene are hydrates that contain between 9 and 21 water molecules in their crystal structures. In this study, the percentage water of crystallization was measured by TG analysis (Fig. 2) and Karl Fisher titration, and the results (Table 1) were of the same as that reported by previous investigators [16,20]. Determining the water content was important to ensure accurate reporting of the molar concentration of calixarenes in solution. Nifedipine is practically insoluble in water, 4–5 $\mu g.ml^{-1}$, and the solubility only increase slightly with an increase in pH (3.9 ± 0.1 $\mu g.ml^{-1}$ at pH 5, 4.4 ± 0.1 $\mu g.ml^{-1}$ at pH 7, and 5.1 ± 0.1 $\mu g.ml^{-1}$ at pH 12). These measured solubility values agreed with those reported by other researchers

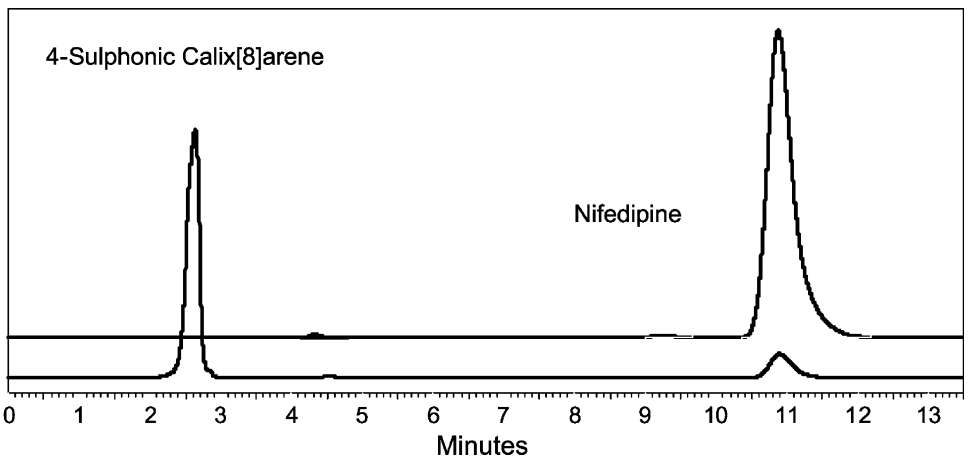

Fig. 3. HPLC chromatograms of nifedipine and nifedipine in the presence of 4-sulphonic calix[8]arene.

Table 1
Molecular weight, number of repeating phenolic units, cavity size, and water content of the 4-sulphonic calix[*n*]arenes

Number of phenolic units	Molecular weight	Cavity size (Å)[a]	TG crystal H_2O (%)	Reported H_2O (%)[b]	KF water content (%)	Stoichiometric calixarene:H_2O ratio
4	745	3.0	18	20	17 ± 1.6	1:9
6	1117	7.6	17	14	16 ± 1.2	1:13
8	1489	11.7	20	–	19 ± 1.5	1:21

[a] Gutsche, C.D. [8]; Zhang et al. [22].
[b] Zhang et al. [16]; Arena et al. [20].

[1,2]. The 4-sulphonic calix[*n*]arenes are water-soluble and their aqueous solubilities are at least 0.1 M [8].

3.1. Solubility profiles of nifedipine in the presence of 4-sulphonic calix[4]arene and 4-sulphonic calix[8]arene

Phase solubility profiles measured at 30 °C and pH 5, 7, and 12 of the amount of nifedipine solubilized versus the concentration of 4-sulphonic calix[*n*]arene are shown in Figs. 4–6. The effect of the calixarenes on the solubility of nifedipine depended on the size of calix[*n*]arenes and the pH of the medium. In the presence of calix[4]arene, A_L (linear, indicating the formation of 1:1 nifedipine:calixarene complexes), A_P (parabolic positively deviating curve, indicating the formation of 1:2 nifedipine:calixarene complexes), and A_N (negatively deviating curve) diagrams were observed at pH 5, 7 and 12, respectively. In the presence of calix[8]arene, A_L diagrams were observed at all three pH values. The largest increase in solubility from $(1.11 \pm 0.03) \times 10^{-5}$ M to $(3.28 \pm 0.03) \times 10^{-5}$ M was observed at 0.008 M 4-sulphonic calix[8]arene and pH 5. At both pH 5 and 7, the 4-sulphonic calix[8]arenes solubilized nifedipine better than 4-sulphonic calix[4]arene ($P < 0.0001$). There was no significant difference in the increase in solubility caused by 4-sulphonic calix[4]arene and 4-sulphonic calix[8]arene at pH 12.

The increased solubility of nifedipine in the presence of 4-sulphonic calix[*n*]arenes indicated that calixarenes might form complexes with nifedipine. According to Higuchi and Connors [19] the linear increases in solubility seen in these graphs, Type A phase solubility profiles, could be due to one or more molecular interactions between the nifedipine and the calixarenes to form distinct chemical species which may be called soluble nifedipine:4-sulphonic calix[*n*]arene complexes. Results for the linear regression analysis of the phase solubility profiles are listed in Table 2. Furthermore, since all the slopes of the Type A_L diagrams were less than unity it was assumed that 1:1 complexes were formed in the presence of calix[8]arene at all three pH values and calix[4]arene at pH 12. A_P diagram indicated 1:2 complexes were produced in the presence of calix[4]arene at pH 5. The A_N diagram shown at pH 7 is problematic and difficult to interpret. The negative deviation from linearity may be associated with ligand-induced changes in the dielectric constant of the water or self-association of the ligand at high calixarene concentrations [19].

Even when no evidence is available to indicate that a one-to-one complex is formed, it is common practice to calculate $K_{1:1}$ for all Type A diagrams in order to facilitate comparison of complexing tendencies [19]. So, stability constants for A_L profiles (Table 2) were calculated according to the following equation: $K_{1:1} = \text{slope}/S_0$ (1-slope), where S_0 is the solubility of nifedipine in the absence of calix[*n*]arenes. Type A_P diagram was represented by a value $K_{1:1}$ calculated from the best overall

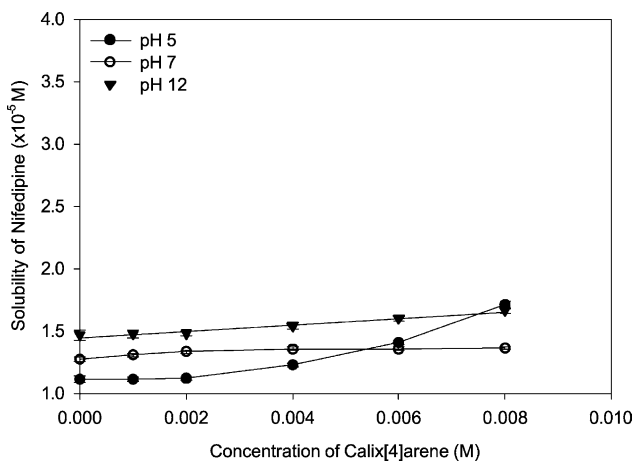

Fig. 4. Phase aqueous solubility profiles of nifedipine in the presence of 4-sulphonic calix[4]arene at 30 °C.

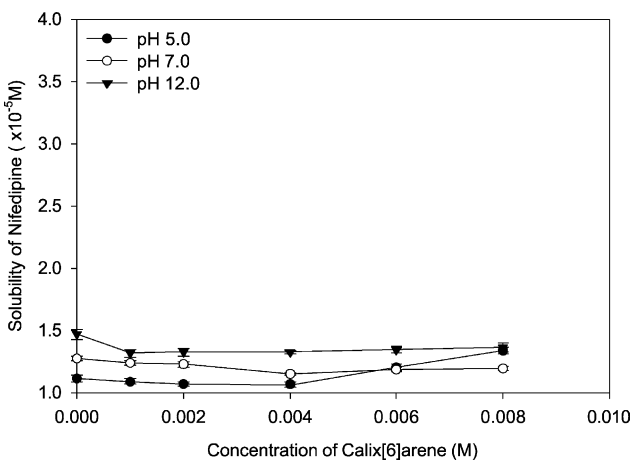

Fig. 5. Phase aqueous solubility profiles of nifedipine in the presence of 4-sulphonic calix[6]arenes at 30 °C.

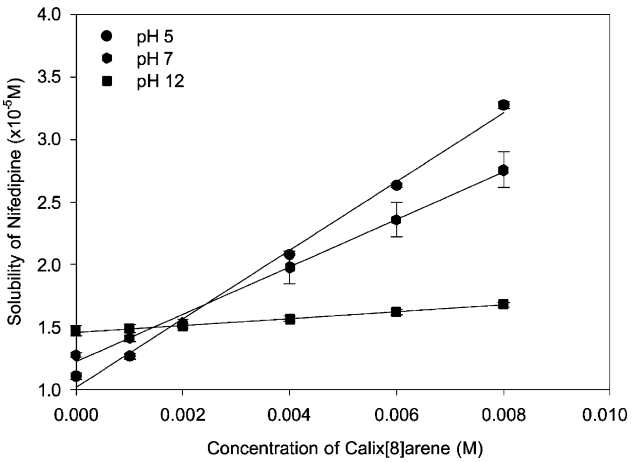

Fig. 6. Phase aqueous solubility profiles of nifedipine in the presence of 4-sulphonic calix[8]arenes at 30 °C.

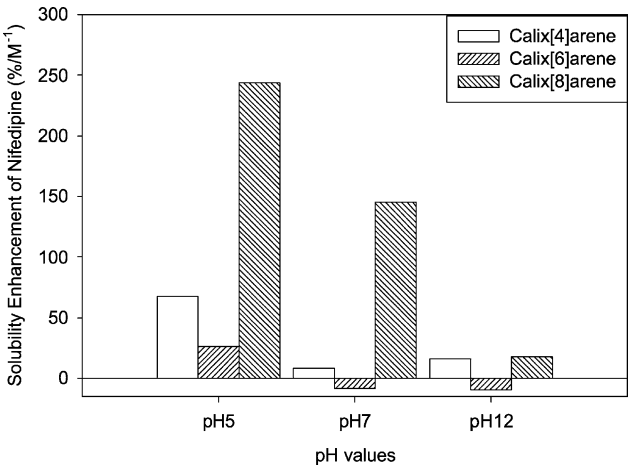

Fig. 7. Mean solubility enhancement ($n = 3$) of nifedipine by 4-sulphonic calix[n]arenes at a concentration of 0.008 M.

linear fit while A_N diagram was represented by an initial linear fit [19]. These stability constants are empirical parameters, which describe approximately the increase in apparent solubility of nifedipine in the presence of the 4-sulphonic calix[n]arenes. Based on the calculated stability constants 4-sulphonic calix[n]arenes with $n = 4$ and 8 formed stable complexes with nifedipine at pH 5.0 ($K_{1:1} = 76.2\ M^{-1}$ when $n = 4$; $K_{1:1} = 247.7$ when $n = 8$); at pH 7.0 calix[8]arene formed very stable complexes ($K_{1:1} = 148.5\ M^{-1}$) while calix[4]arene formed relatively stable complexes ($K_{1:1} = 23.3\ M^{-1}$); at pH 12.0, both calix[8]arene and calix[4]arene formed relatively stable complexes ($K_{1:1} \approx 18\ M^{-1}$).

3.2. Solubility profiles of nifedipine in the presence of 4-sulphonic calix[6]arene

In the presence of 4-sulphonic calix[6]arene, the solubility of nifedipine was smaller than in the absence of the oligomer. A greatest decrease in solubility from $(1.47 \pm 0.04) \times 10^{-5}$ M to $(1.33 \pm 0.02) \times 10^{-5}$ M was observed at 0.002 M 4-sulphonic calix[6]arene and pH 12.0. But at higher concentrations of calix[6]arene (0.004–0.008 M) and lower pH 5.0, the solubility of nifedipine improved compared to the solubility in the absence of calixarene ($P < 0.05$).

Table 2
Linear regression parameters of the Type A_L phase solubility profiles and apparent stability constants for complexes of nifedipine and the 4-sulphonic calix[n]arenes

pH	Calix[n]arene	Slope ($\times 10^{-5}$M)	R^2	Type of solubility profiles	$K_{1:1}$ (M^{-1})
5.0	4	73.18	0.9243	A_P	76.2
	8	274.88	0.9946	A_L	247.7
7.0	4	29.61	0.9964	A_N	23.3
	8	189.26	0.9954	A_L	148.5
12.0	4	25.41	0.9754	A_L	17.3
	8	27.28	0.9967	A_L	18.6

3.3. Solubility enhancement of nifedipine by 4-sulphonic calix[n]arenes

The solubility enhancement of nifedipine by 0.008 M 4-sulphonic calix[n]arenes at different pH values were calculated by the following equation: $(S - S_0)/S_0/0.008$ where S and S_0 was the solubility of nifedipine in the presence and in the absence of calix[n]arenes, respectively. The data was plotted in Fig. 7. It showed 4-sulphonic calix[8]arene enhanced the solubility of nifedipine the most at all three pH values, followed by 4-sulphonic calix[4]arene. But 4-sulphonic calix[6]arene decreased the solubility in most cases.

Overall, 4-sulphonic calix[6]arene decreased the solubility of nifedipine while 4-sulphonic calix[4]arene and calix[8]arene increased the solubility with calix[8]arene having the greatest effect. Based on the calculated stability constants the solubilization of nifedipine by complexation with 4-sulphonic calix[n]arenes depended on the pH of solution, number of phenolic groups in the calix[n]arene ring and the calixarene concentration. The calculated stability constants also showed that calix[8]arene was the best solubilizing agent for nifedipine, especially at lower pH.

4. Discussion

Since the solubility of nifedipine was not significantly changed with an increase in pH from 5 to 12 but did significantly increase when various concentrations of three 4-sulphonic calix[n]arenes were added to the solutions, it was clear that the calixarenes must in some way interact with nifedipine–calixarene

associations. This interaction was not micellar aggregation of the calixarenes around the nifedipine molecules because the sulphonated calix[*n*]arenes does not aggregate at concentrations less than 0.2 M in water [21]. The concentrations of 4-sulphonic calix[*n*]arenes used in this study, Figs. 4–6, were therefore below the critical micelle concentrations.

Eliminating micellar solubilization the increased nifedipine solubility must be due to complexation between the drug and the calixarenes afforded by weak forces including hydrogen bonding, π–π interactions, electrostatic interactions, or dipole–dipole moments [22]. With the help of these forces nifedipine most probably form non-covalent inclusion complexes with the 4-sulphonic calix[*n*]arenes similar to the complexes it forms with cyclodextrins [5–7]. This is possible because the hydrophobic and hydrophilic properties and the inner cavity diameters, Table 1, of the 4-sulphonic calix[*n*]arenes are similar to that of the α-, β-, γ-cyclodextrins [15,22]. The inter cavity diameter of 4-sulphonic calix[4]arene is slightly smaller than that of at α-cyclodextrins (5.7 Å), the inner cavity diameter of the calix[6]arene is comparable to that of β-cyclodextrin (7.8 Å), while that of the calix[8]arene is slightly larger than that of γ-cyclodextrin (9.5 Å). The cavity sizes are however not large enough for inclusion of the complete nifedipine molecule into the calixarenes. Based on other studies reporting the size and geometry of the nifedipine molecule and its complexation with cyclodextrins, the complex-forming moiety of nifedipine might be the 2′-nitrophenyl group; the dimensions of which would be more geometrically compatible with a closer and stronger interaction with the calixarenes cavities [6,7].

4.1. Hydrogen bonding

Hydrogen bonding is one of the most important forces responsible for the formation of host–guest complexed systems. Solubility measurements at different pH provide one way to study the contribution of H-bonds in forming complexed molecular species [19]. 4-Sulphonic calix[*n*]arenes contains free intra-annular OH groups, which means the complexation mechanism could involve hydrogen bonding between the phenolic hydrogen atoms of the calix[*n*]arenes and the nitrogen atom on the dihydropyridine ring of nifedipine similar to the interactions between nifedipine and substituted phenolic ligands [1]. Since the pH of the solution influences the dissociation of the calixarene phenolic groups and therefore the extent of the hydrogen bonding of the hydroxyls, it determines the extent of complexation between nifedipine and the hydrophobic cavity of the calix[*n*]arenes [16].

At pH 5 the phenolic groups are not dissociated and are available to form hydrogen bonds with the nifedipine, increasing the solubility as shown in Fig. 7. At pH 12, most of the phenolic groups are dissociated and are therefore not available to form hydrogen bonds with nifedipine limiting the increase in solubility as shown in Fig. 7. In addition, earlier studies have showed that at high pH the phenolate groups on the lower rim of the 4-sulphonic calix[*n*]arenes form stronger intra-molecular hydrogen bonds leading to more fixed conformations while at low pH the phenolic units are more flexible and randomly oriented due to weaker intra-molecular bonds [11,12]. Thus, at higher pH the stronger intra-molecular hydrogen bonding reduced complexation and the ability to solubilize nifedipine. This mechanism was supported by our solubility data and calculated stability constants, Fig. 7 and Table 2, which showed that the 4-sulphonic calix[*n*]arenes increased the solubility of nifedipine significantly more at lower compared to higher pH.

4.2. Hydrophobic bonding

Hydrophobic bonding is a term applied to attractive forces between non-polar (usually hydrocarbon) molecules or portions of molecules. Although these forces are small, large solvent-solvent intermolecular attractive forces enhance them when the molecules are in a polar medium such as water [19]. Nifedipine, a highly hydrophobic molecule, is in a sense ‘squeezed out’ of the polar phase by its high internal pressure, leading to an appreciable degree of interaction between nifedipine and the non-polar hydrophobic cavity of calixarenes. Although hydrophobic interactions are limited by the cavity size of calixarenes, Shinkai et al. [13] showed that ‘host-size selectivity’ does exist in host-guest type complexation with calixarenes. According to the inner cavity diameters listed in Table 2 it is expected that the larger calix[8]arene cavity would geometrically be more suited for a closer and stronger interaction with nifedipine than the smaller calix[4]arene cavity. This was confirmed by the higher solubility afforded by 4-sulphonic calix[8]arene (Fig. 6) compared to 4-sulphonic calix[4]arene (Fig. 4). Solubility differences as a function of cavity size also suggests that based on the molecular structure of nifedipine, the complexes between the sulphonated calixarenes and this neutral molecule should be classified as intermolecular complexes [23].

4.3. Electron donor–acceptor interaction

In addition to the hydrogen bonding and hydrophobic bonding, nifedipine complexation with 4-sulphonic calix[*n*]arenes could also be facilitated by an electron donor–acceptor interaction involving the π orbitals of the calixarene aromatic nucleus with those of either the nifedipine dihydropyridine or nitrobenzene ring system [24–26]. However, although this mechanism of complexation cannot be excluded, the results obtained in this study do not provide enough evidence for this kind of interaction.

4.4. Conformational effect

The conformation of calixarenes in solution varies with the number of the phenolic units [8]. This may affect the formation of hydrogen bonding between calixarenes and nifedipine. Especially, the conformation of calix[6]arenes in solution has been the subject of considerable study and some controversy [9,27]. The consensus is that depending on the pH of the solution a strong deviation from the cone conformation is observed in the structure of the 4-sulphonic calix[6]arene [27,28]. Based on X-ray structure analysis and molecular modeling studies at neutral pH the molecule exists as an anionic host and the most stable conformation is a double partial (pinched) cone [9,27] which is less stable than the cone conformation and pleated loop conformation [9]. The decreased solubility obtained for nifedipine showed that the possible interaction between 4-sulphonic calix[6]-arene and the drug molecule are different from 4-sulphonic calix[4]arene and calix[8]arene. But an increase in solubility was observed only at the highest concentration (0.008 M) and lowest pH 5. Conformational changes in the calix[6]arene molecule might attribute to its unusual effect on the solubility of nifedipine.

Calix[4]arenes normally exist in a cone conformation (Fig. 1), which is mainly maintained by the cyclic array of four intra-molecular bonds [9]. The calix shape of the molecule completely disappears in most calix[8]arenes and a new conformation which has the architecture of a pleated loop is observed [9,23]. Moreover, space-filling models suggest that the cyclic octamer is more flexible than the cyclic tetramer due to stronger intra-molecular hydrogen bonding in the calix[4]arenes [8]. This means that the smaller calix[4]arenes have the strongest intra-molecular hydrogen-bonding which would reduce its ability to form hydrogen bonds with nifedipine [23]. Solubility results, Figs. 4 and 6, and stability constants, Table 2, confirmed that the 4-sulphonic calix[8]arene which has a more flexible conformation solubilized significantly more nifedipine than calix[4]arene which is more rigid and forms fewer intermolecular hydrogen bonds [8].

5. Conclusions

To conclude, the solubilizing effect of 4-sulphonic calix[*n*]arenes on the solubility of nifedipine showed that the size of the 4-sulphonic calix[*n*]arenes, the pH of solubility medium, and the concentration of the calix[*n*]arenes all significantly influenced the solubility of nifedipine. 4-sulphonic calix[8]arene improved the solubility of nifedipine the most, about 3 times the control at 0.008 M and pH 5, followed by 4-sulphonic calix[4]arene, about 1.5 times the control at 0.008 M and pH 5, while 4-sulphonic calix[6]arene decreased the solubility of nifedipine.

The possible mechanisms involved in the complexation between 4-sulphonic calix[*n*]arenes and nifedipine may be a combination of hydrogen bonding, hydrophobic bonding, and possibly electron donor–acceptor interactions. However, the degree to which these forces promote the formation of nifedipine:4-sulphonic calix[*n*]arene complexes with increased solubility was limited by conformational changes in the 4-sulphonic calix[*n*]arene molecules. The conformation of the calix[*n*]arene molecules differed due to differences in the size of the supramolecular structures and changes in the degree of phenolic hydroxyl dissociation with a change in pH.

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