Studies of ternary systems of sulfadiazine with β-cyclodextrin and aminoacids

Estudios de sistemas ternarios de sulfadiazina con β-ciclodextrina y aminoácidos

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ABSTRACT

Introduction: Cyclodextrins (CD), are known to form inclusion complexes with a variety of guest molecules both in solution and in the solid state. This can lead to the alteration of properties of guest molecules. Unfortunately, the complexation efficiency of CD is rather low, and can be enhanced by formation of ternary complexes using aminoacids (AA). Sulfadiazine (SDZ) is an antibiotic with extremely low water solubility which limits its therapeutic applications and bioavailability.

Objectives: The aim of this work was to increase the aqueous solubility of SDZ by preparing ternary complexes of this drug with β-cyclodextrin (βCD) and an AA as a third auxiliary substance.

Materials and Methods: Complex formation was studied by phase solubility analysis (PSA), nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC), thermogravimetric analysis (TG) and scanning electron microscopy (SEM).

Results: The apparent stability constants (K_C) of the multicomponent complexes were calculated from the solubility diagrams. By the analysis of the NMR spectra, it could be said that the shifts of some protons evidenced the important role of the AA in the formation of multicomponent complexes. Among the AA, Arginine (ARG) proved to have better solubilizing properties for SDZ, reaching an improvement up to 70 times. The use of DSC, TG and SEM suggested the formation of new solid phases between SDZ:βCD:AA.

Conclusions: As a result of this research, it was determined that ternary products were more effective in improving drug solubility than the corresponding SDZ:βCD binary system.

Keywords: sulfadiazine; complexation; β-cyclodextrin; ternary systems; aminoacid.
Conclusiones: Como resultado de esta investigación, se determinó que los productos ternarios fueron más eficaces en la mejora de la solubilidad del fármaco que el sistema binario SDZ: βCD.

Palabras Claves: sulfadiazina; complejación; β-ciclodextrina; sistemas ternarios; aminoácidos.

INTRODUCTION

CD (Fig. 1A), cyclic oligosaccharides joined through 1-4 bonds, are known to form inclusion complexes with a variety of guest molecules. This can lead to the alteration of physical, chemical and biological properties of guest molecules, and can eventually have considerable pharmaceutical potential. Thus, the hydrophilic CD have been extensively used to enhance the oral bioavailability of several drugs. These improvements are mainly ascribable to the increase in solubility and wettability of the drugs through the formation of inclusion complexes. Unfortunately, the complexation efficiency of CD is rather low, and consequently significant amounts of these oligosaccharides are needed to solubilize small amounts of water-insoluble compounds. However, enhanced CD solubilizing capacity can be obtained by formation of ternary complexes between a drug molecule, a CD molecule and a third component. Among the different strategies used for this purpose, studies carried out in our laboratory have demonstrated that the solubility capacity of the CD was significantly enhanced when ethanolamines, meglumine and aminoacids were incorporated as ternary components in the complexes. On the other hand, other works showed that the addition of aminoacids can increase the solubilizing and complexing abilities of CD by multicomponent complex formation.

SDZ (Fig. 1B) is derived from sulfanilamide, which is similar in structure to para-aminobenzoic acid (PABA), a factor required by bacteria for folic acid synthesis. SDZ competitively inhibits dihydropteroate, the bacterial enzyme that is responsible for the incorporation of PABA into dihydrofolic acid, the immediate precursor of folic acid. A drawback, which restricts the application of this compound, is its extremely low water solubility (only about 0.074 mg/ml at 25°C), which limits its therapeutic applications and bioavailability.

Studies involving the complexation of SDZ with CD in binary systems have been reported in the literature, including our previous results. These investigations have demonstrated that using complexation with CD (βCD, HPβCD or MβCD) can improve the aqueous solubility of SDZ. Also, a clear influence of the complex preparation methods on the drug dissolution behavior was observed. In this context, it seemed of interest to continue our studies on new types of drug carriers by obtaining ternary complexes of SDZ and βCD with the addition of AA such as glycine (GLY), leucine (LEU), aspartic acid (ASP), glutamic acid (GLU) and ARG, as a strategy to improve the CD solubilizing power.

Fig.1. Chemical structure and proton atom numbering scheme of: (A) β-cyclodextrin, (B) Sulfadiazine, (C) Glycine, (D) Arginine and (E) Glutamic acid.

MATERIALS AND METHODS

Materials

SDZ was obtained from Parafarm (Buenos Aires, Argentina). D2O 99.9 atom % D used in spectroscopic studies, L-Leucine and L-Arginine were purchased from Sigma. L-Aspartic Acid and L-Glutamic Acid were obtained from Anedra (Buenos Aires, Argentina). Glycine was purchased from Todo Droga (Córdoba, Argentina) and βCD was a gift from Ferromet S.A. [agent in Argentina of Roquette (Lestrem, France)].

The water used in these studies was generated with a Milli-Q Water Purification System (Millipore Bedford, USA). All other chemicals and solvents used were of analytical grade.
Phase solubility analysis (PSA)

Solubility diagrams were obtained according to Higuchi and Connors.\(^\text{18}\) These studies were done using excess amounts of SDZ either with constant quantities of βCD (4.2 mM) and different concentrations of the AA: LEU (0-138 mM), GLY (0-55.7 mM), ARG (0-179 mM), ASP (0-37 mM) and GLU (0-37 mM), or with constant amounts of the AA: LEU (28 mM), ARG (28 mM), GLU (7.5 mM), ASP (7.5 mM) and GLY (28 mM) and different concentrations of βCD (0-12.0 mM). Then, the resulting suspensions were sonicated in an ultrasonic and placed in a 25.0±0.1°C thermostatized water bath for 72 h. After equilibrium was reached, the suspensions were filtered through a 0.45 µm membrane filter (Millipore®, USA) and analysed by UV–Vis spectrophotometry (Shimadzu UV 260 UV-visible spectrophotometer) at 264 nm. Each experiment was repeated at least three times and the results reported were the mean values. The apparent stability constant (K\(_{C}\)) values for the corresponding SDZ:CD:AA systems were calculated from the slope of the phase-solubility diagrams and S\(_0\) (solubility of SDZ at 25 °C in absence of complexing agents) according to equation (1)\(^\text{18}\):

\[
K_C = \frac{\text{slope}}{S_0 (1-\text{slope})} \quad (1)
\]

Nuclear Magnetic Resonance Studies (1H NMR)

All experiments were performed on a Bruker Advance II High Resolution Spectrometer. Spectra were measured at 400.16 MHz and 298 K using D\(_2\)O, with the chemical shift of the residual solvent at 4.8 ppm being used as an internal reference. Induced changes in the 1H chemical shifts (Δδ) for βCD, AA and SDZ were originated from their complexation, and calculated using the following equation (Eq. 2):

\[
\Delta\delta = \delta_c - \delta_0 \quad (2)
\]

where δ\(_0\) and δ\(_c\) are the chemical shifts of the pure compounds and the ternary complexes, respectively.

Positive and negative signs refer to downfield and upfield shifts, respectively.

Two-dimensional Rotating Frame Overhauser Experiments (2D ROESY)

Drug and AA inclusion in the βCD cavity was studied by 2D ROESY. Pulse sequence: roesygpph19; 2D ROESY with cw spinlock for mixing; phase sensitive and water suppression using 3-9-19 pulse sequence with gradients; p15 (f1 channel), pulse for ROESY spinlock (200000 usec); d1:2 sec, d19 (delay for binomial water suppression), d19 = (1/(2*d)), d = distance of next null (in Hz) use gradient ratio: gp 1:gp 2 (30:30); for z-only gradients: gpz1: 30%; gpz2: 30% use gradient files; gpnam1: SINE.100, gpnam2: SINE.100. Before Fourier transformation, the matrix was zero filled to 4096 (F2) by 2048 (F1), and Gaussian apodization functions were applied in both dimensions. A ROESY experiment is suitable for obtaining information about the spatial proximity between the atoms of the host and the guest molecules by observing the intermolecular dipolar cross-correlations.

Preparation of the SDZ:βCD:AA systems in the solid state

The ternary systems (SDZ:βCD:AA) were prepared with equimolar ratios of SDZ, βCD and ARG, GLU or GLY. The physical mixtures were prepared by the simple mixing of the components, while the co-evaporation systems by mixing and dissolving the corresponding components, in ethanol:water (1:1) mixtures, and removing the solvent with ultrasound. In freeze-drying systems, the components were suspended in distilled water, and then sonicated until complete dissolution of the drug. Solutions were frozen before the freeze-drying was started (Freeze Dye 4.5 Labconco corp., Kansas City, MI). Also, the pure compounds were lyophilized prior to DSC, TG and PXRD studies.

Differential scanning calorimetry (DSC) and Thermo-gravimetric analysis (TG)

The DSC analyses were carried out with a DSC TA 2920 using a heating rate of 10°C/min from 25 up to 350°C and under a nitrogen flow.

The TG curves were obtained using a TG TA 2950 under the same conditions as those of DSC.

Scanning electron microscopy (SEM) studies

The microscopic structures were investigated using a scanning electron microscope LEO Model EVO 40XVP. The samples were fixed on a brass stub using double-sided aluminum tape, which were then made electrically conductive by coating with gold.

RESULTS AND DISCUSSION

Phase solubility analysis (PSA)

The PSA were performed with SDZ and increasing concentrations of each AA. It was observed that with LEU, GLY, ASP and GLU, the addition of the AA did not change the SDZ solubility and therefore its concentration in solution. This behavior suggested that the drug was found in its solubility limit in the range of the AA concentrations studied, leading to think that no interaction occurred between
them. However, an interaction between SDZ and ARG was observed since an increase in the solubility value to 27.25 mg/ml was achieved. The $K_C$ value from the linear solubility isotherm was also determined following the method of Higuchi and Connors. Intrinsic solubility ($S_0$), maximum solubility ($S_{\text{max}}$), and solubility efficiency (ES, $S_{\text{max}}/S_0$) values were determined from PSA and are presented in Table 1. Since the presence of ARG were observed fluctuations in the pH values of the solutions (around 8) during the process, and in order to conduct the study at the same pH, the PSA was carried out using a buffer solution of pH 8.

Then, the affinity of the drug for both the βCD and the AA, was determined by PSA in water. In an initial screening, the influence of changes in the concentration of the AA with βCD constant and SDZ in excess was evaluated. No variations were observed in the aqueous solubility of the drug, except for ARG (Table 1). When this AA was added as a third component, a higher enhancement in the solubility of SDZ was obtained in comparison with the binary complex (SDZ:βCD) as a result of the potential ability of the basic aminoacid to simultaneously interact with both the βCD and the drug. Also, a higher enhancement in the $K_C$ for the ternary SDZ:βCD:ARG complex was obtained in comparison with both binary systems (SDZ:ARG and SDZ:βCD), as shown in Table 1.

Finally, in a further attempt to improve the solubilizing and complexing ability of βCD, phase-solubility studies of the drug were performed in the presence of increasing concentrations of βCD with a constant concentration of the AA. In all ternary systems with aminoacids, the isotherms were linear within the βCD concentration ranges studied, with all the slopes less than 1, except for ARG. The $K_C$ values obtained (Table 1) showed that the binding of SDZ with βCD in the presence of GLU was relatively lower than with the other AA or βCD alone. These findings suggest that the presence of GLU weakens the interaction between SDZ and βCD. Nevertheless, it is interesting to note that the solubility of the drug in the ternary system with this AA increases to 0.678 mg/ml due to the formation of a highly soluble complex. This event can be explained by the higher initial solubility of the drug due to the increased ionization in the presence of GLU, with a consequent decrease in affinity for the apolar cavity of the βCD. The same reasoning could be applied to justify the increase in solubility caused by the presence of ASP as both AA, GLU and ASP, have one of the carboxylic acid groups ionized at the pH of the determinations.

Although the $K_C$ values for the SDZ:βCD:LEU and SDZ:βCD:GLY systems were greater and lower, respectively, than that of SDZ:βCD, the solubility results were very similar for the three systems.

### Table 1: Data from the phase solubility analysis of SDZ with βCD and different AA

<table>
<thead>
<tr>
<th>System</th>
<th>Solvent</th>
<th>final pH</th>
<th>$K_C$ (M⁻¹)</th>
<th>$S_0$ (mg/ml)</th>
<th>$S_{\text{max}}$ (mg/ml)</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDZ:βCD</td>
<td>water</td>
<td>5.96</td>
<td>282 ± 11</td>
<td>0.073 ± 0.009</td>
<td>0.33 ± 0.02</td>
<td>4</td>
</tr>
<tr>
<td>SDZ:ARG</td>
<td>Buffer solution pH 8</td>
<td>8.77</td>
<td>395 ± 6</td>
<td>0.90 ±0.06</td>
<td>27.2 ±0.5</td>
<td>30</td>
</tr>
<tr>
<td>SDZ:βCD:ARG</td>
<td>water</td>
<td>8.49</td>
<td>1156 ±94</td>
<td>0.073 ±0.009</td>
<td>13.18 ±0.03</td>
<td>70</td>
</tr>
<tr>
<td>SDZ:βCD:GLI</td>
<td>water</td>
<td>5.78</td>
<td>258.4 ± 0.3</td>
<td>0.073 ± 0.009</td>
<td>0.40 ± 0.09</td>
<td>5</td>
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<tr>
<td>SDZ:βCD:LEU</td>
<td>water</td>
<td>6.14</td>
<td>389 ± 7</td>
<td>0.073 ± 0.009</td>
<td>0.32 ± 0.01</td>
<td>4</td>
</tr>
<tr>
<td>SDZ:βCD:ASP</td>
<td>water</td>
<td>3.19</td>
<td>105 ± 5</td>
<td>0.073 ± 0.009</td>
<td>0.62 ± 0.01</td>
<td>8</td>
</tr>
<tr>
<td>SDZ:βCD:GLU</td>
<td>water</td>
<td>3.45</td>
<td>122 ± 7</td>
<td>0.073 ± 0.009</td>
<td>0.68 ± 0.04</td>
<td>9</td>
</tr>
</tbody>
</table>

### H NMR Studies

$^1$H NMR spectroscopy is an analytical tool frequently used to study the inclusion of guest molecules in a host because this fact modifies the environment of both, the included protons of the guest moiety and those of the host cavity.

It is well known that βCD has the topology of a hollow cone shape, with the H3 and H5 being inner protons. The inclusion of SDZ and the AA in the βCD cavity was first evaluated by the changes in the chemical shifts (δ) of the protons in the complex regarding the free entities. For the NMR studies, ARG, GLU and GLY as model AA were selected. Table 2 presents the assignments of the SDZ, AA and βCD peaks and the chemical shift deviations ($\Delta$δ) due to complexation (see numbering of proton in Fig. 1).
### Table 2. Chemical shifts for the protons of sulfadiazine (SDZ), β-cyclodextrin (β-CD) and the aminoacids glycine (GLI), arginine (ARG) and glutamic acid (GLU), in the free and complex forms

<table>
<thead>
<tr>
<th></th>
<th>β-CD-SDZ-GLI*</th>
<th>β-CD-SDZ-ARG**</th>
<th>β-CD-SDZ-GLU*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>3.9147</td>
<td>3.9147</td>
<td>3.9147</td>
</tr>
<tr>
<td>H2</td>
<td>3.2293</td>
<td>3.2293</td>
<td>3.9649</td>
</tr>
<tr>
<td>H3</td>
<td>1.7520</td>
<td>1.7520</td>
<td>3.9491</td>
</tr>
<tr>
<td>H4</td>
<td>1.7520</td>
<td>1.7520</td>
<td>3.9491</td>
</tr>
<tr>
<td>H5</td>
<td>1.7520</td>
<td>1.7520</td>
<td>3.9491</td>
</tr>
<tr>
<td>H6</td>
<td>1.7520</td>
<td>1.7520</td>
<td>3.9491</td>
</tr>
</tbody>
</table>

Δδ = δc - δ0

**D2O, pH 9.0**

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**complex forms**

<table>
<thead>
<tr>
<th></th>
<th>ACID-SDZ-GLI*</th>
<th>ACID-SDZ-AR**</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>3.9147</td>
<td>3.9147</td>
</tr>
<tr>
<td>H2</td>
<td>3.2293</td>
<td>3.2293</td>
</tr>
<tr>
<td>H3</td>
<td>1.7520</td>
<td>1.7520</td>
</tr>
<tr>
<td>H4</td>
<td>1.7520</td>
<td>1.7520</td>
</tr>
<tr>
<td>H5</td>
<td>1.7520</td>
<td>1.7520</td>
</tr>
<tr>
<td>H6</td>
<td>1.7520</td>
<td>1.7520</td>
</tr>
</tbody>
</table>

Table 2. Chemical shifts for the protons of sulfadiazine (SDZ), β-cyclodextrin (β-CD) and the aminoacids glycine (GLI), arginine (AR**G**), and glutamic acid (GLU**G**), in the free and complex forms.
The upfield shifts observed for H5 and H3 protons of βCD, localized at the internal surface of the cavity, showed the presence of host-guest interactions for the SDZ:βCD:GLY system. The chemical shifts corresponding to the protons located on the external surface of βCD (H1, H2 and H4) were also modified. In the presence of βCD and GLY, all SDZ protons were shifted downfield, with the exception of Ha that was shifted upfield. GLY protons were shifted downfield.

However, when βCD was in the presence of the drug and ARG, as a third component, a small shift for H3 and a downfield displacement for H5 were only produced. In addition, the δ corresponding to the protons located at the outer surface of βCD (H1, H2 and H4) were also modified. As for SDZ, deshielding effects were observed for Hb, Hc and Hd but upfield shifts for Ha. Downfield effects were found for all ARG protons.

Also, downfield displacements were found for H3 and H5 of βCD in the SDZ:βCD:GLU complex. As in the cases above, the δ of the three external protons of βCD were also modified and downfield effects for Hb, Hc and Hd, and an upfield effect for Ha of SDZ were observed. Upfield shifts were found for all GLU protons.

The downfield shifts observed for H3 and H5 of βCD when GLU was present, and only for H5 when using ARG, could be attributed to the weak interactions (van der Waals force) between the hydrogen atoms of the internal cavity of the βCD with the drug or the AA. Differences were observed between the binary and the ternary complexes. In the former case, a higher displacement was observed for H3, while in the latter case, the H5 showed the greatest displacement. On the other hand, the upfield shifts observed for both internal protons of βCD when GLY was present, were also evidence of host-guest interactions. These last shifts are probably due to the anisotropic currents produced by the aromatic ring of SDZ, which can indicate the deep penetration of the drug into the CD cavity.

The formation of a complex by inclusion is clearly evidenced by these spectral changes of the inner protons H3 and H5 of βCD in the presence of both, the drug and the AA. Furthermore, the shifts observed for the protons located on the outer surface of the oligosaccharide, may be due to a conformational arrangement of the guest molecule or an effect produced by the presence of the AA.

Also, the upfield shift showed by the Ha of the drug is due to its association with the oxygen atoms of the CD, rich in π electrons, while the downfield shifts observed for the other protons are probably caused by a variation of the local polarity or by the deshielding effect produced by the Van der Waals forces between the drug and the carbohydrate chains.

Continuing with the analysis of the NMR spectra, it could be said that the shifts of the protons belonging to the AA suggest the involvement of them in the interactions between the βCD and SDZ, evidencing the important role of these AA in the formation of multicomponent complexes.

**ROESY Experiments**

2D ROESY experiments were carried out to investigate the inclusion of SDZ and/or AA in the βCD cavity. ARG, GLU and GLY were also used as third components for these studies. Figure 2 shows the partial contour plots of 2D ROESY spectra for the studied systems. In the SDZ:βCD:GLY system (Fig. 2A), cross-peaks were observed between Ha of SDZ and some protons of βCD and some protons of βCD (H5 and H6) as well as between Hb and H3, H5, and H6, indicating the formation of an inclusion complex in which the ring A of SDZ was deeply inserted into the hydrophobic cavity of the host. Furthermore, H1 of GLY correlated with Ha and also with Hb of SDZ, but the latter with a low intensity.

However, in the 2D ROESY of SDZ:βCD:ARG (Fig. 2B), Ha and Hb of the drug correlated with the inner proton H5 and with H6 of βCD, and also with H3 of ARG. As in the previous case, the formation of a complex was postulated through the insertion of the aromatic ring A of SDZ into the host cavity. In addition, the interaction of ARG with the drug was observed.

Finally, in the SDZ:βCD:GLU system (Fig. 2C), it was also observed the insertion of the drug in the CD cavity through the ring A since Ha of SDZ correlated with H5 and H6 of βCD. However, no interaction with GLU was observed.

The evaluation of the interaction of SDZ with each AA in the presence of βCD by 2D ROESY confirmed that there are associations between them, and that they contribute to the formation of ternary complexes.
Differential scanning calorimetry (DSC) and Thermogravimetric analysis (TG)

The DSC and TG curves of pure compounds and the three ternary systems are shown in Fig. 3 (A, B and C). The thermal curve of SDZ showed a sharp fusion endothermic event occurring at 263 °C, corresponding to the melting point of the drug, followed by an exothermic event attributed, on the basis of TG results, to its thermal decomposition. As observed in TG curves, βCD loses water at temperatures between 25 and 100 °C, with decomposition above 300 °C. The three AA show sharp endothermic melting peaks occurring at 220, 252 and 208 °C for ARG, GLY and GLU, respectively, followed by decomposition, which is consistent with the observations by TG.

When analyzing the physical mixtures with the three studied AA, we found the same characteristic events observed for each of the pure compounds. Therefore, no inclusion complexes were obtained. However, in the solids obtained by both co-evaporation and freeze-drying, the disappearance of the SDZ melting point in all products suggests the formation of true inclusion complexes. Furthermore, the endothermic peak assigned to the dehydration of the βCD shifted to lower temperatures with respect to the pure βCD. This fact can be attributed to a weak interaction of the water molecules with the βCD due to a better integration of this oligosaccharide with the SDZ and/or AA.
Scanning electron microscopy (SEM)

SEM microphotographs of raw material (SDZ, βCD and AA) and ternary solid systems: SDZ:βCD:GLY, SDZ:βCD:ARG, SDZ:βCD:GLU are reported in Figure 4.

SDZ was present as a series of joined acicular crystals. βCD exhibited three-dimensional parallelogram crystals of irregular size, while GLY (Fig. 4 C) was composed of large plate-like crystals with irregular borders. ARG (Fig. 4 G) showed a plate with minute round crystals and GLU (Fig. 4 K) consisted of parallelograms of irregular size.

In all cases, the physical mixtures showed particles of βCD embedded in SDZ, AA and morphologies comparable with those of the pure compounds, revealing no apparent interaction between the species in the solid state. In contrast, freeze-drying products appeared to be of a lesser crystalline structure with shapes and sizes completely different from those of free raw materials. Thus, it was not possible to differentiate the components demonstrating an apparent interaction in the solid state, which might be indicative of the presence of a new solid phase. Finally, the presence of particles of pure components mixed with particles of different morphologies can be observed in the microphotographs of the systems prepared by co-evaporation. This may be attributed to incomplete complex formation. In conclusion, the drastic changes in the particle shape and aspect in freeze drying products indicate the presence of new solid phases. Although the SEM technique is inadequate to conclude genuine complex formation, the obtained microphotographs support the idea of the achievement of three new components.
CONCLUSIONS

On the basis of the physicochemical characterization techniques described in this work, the complex formation between SDZ, βCD and amino acids (GLY, GLU, ARG, ASP and LEU) was confirmed. Both the stoichiometry and equilibrium constants for the inclusion complexes were evaluated by the phase solubility method. ARG and GLU proved to have better solubilizing properties for SDZ than the other AA, as could be determined by the higher solubility values obtained for both ternary complexes. This improvement up to 70 and 9 times for ARG and GLU, respectively, suggests a significant increase in the complexation efficiency between SDZ and βCD by addition of small amounts of amino acids. According to the NMR data, the formation of inclusion complexes is possible through the insertion of the ring A of the drug into the βCD cavity.

The use of DSC, TG, and SEM enabled us to thoroughly elucidate the solid-state interactions of SDZ:βCD:AA ternary systems and suggested the formation of new solid phases. This allowed us to conclude that there are strong evidences of ternary inclusion complex formation between SDZ, βCD and AA by using freeze-drying and co-evaporation. Taking into account these results, we postulate that the interaction of SDZ with βCD and AA through the formation of inclusion complexes, effectively enhance the solubility of SDZ, which can thus increase its bioavailability and improve its pharmaceutical potential.
REFERENCES


