

# EVIDENCE FOR THE 2:1 MOLECULAR RECOGNITION AND INCLUSION BEHAVIOUR BETWEEN CYCLODEXTRINS AND USUAL DRUGS

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## Introduction

Cinchonine (Cinc) is used for the treatment of malaria and also exhibits antihypertensive effects, [1]. Doxorubicin (Dox) is one of the most powerful anthracycline anticancer drugs, largely employed in the treatment of leukaemia and various solid tumors, [2]. 2-thiophenecarboxylic acid thioureas (Materials (1) to (7)) exhibiting antimicrobial properties and could offer significant advantages in future treatment of multidrug resistant infections, [3, 4].

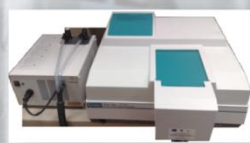
Cyclodextrins (CDs) are macrocyclic oligosaccharides that possess a hydrophobic cavity in which a wide variety of organic molecules can be entrapped forming inclusion complexes. In this work,  $\beta$ -cyclodextrin ( $\beta$ CD), 2-hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD) and  $\gamma$ -cyclodextrin ( $\gamma$ CD) are used as important host compounds. CDs have high molecular recognition ability to complexate guest molecules with suitable dimensions and polarity because of their hydrophobic inner cavity and hydrophilic external surface, [1, 5]. CD usually forms 1:1 complexes with many types of guest molecules. When a guest molecule is bulky or long relative to the dimensions of CD cavity, two CD molecules could be bound to a single guest molecule to form a 2:1 CD-guest nanocapsule-like structure. In the present paper, are presented the results obtained by UV-Vis and DSC measurements.

## Objective

- Determination of the stoichiometric ratio of CD and guest by continuous variation method (UV-Vis data)
- Investigation of the solid complexes for 1:1 and 1:2 molar ratio (guest: host) of combinations between CDs and drugs using DSC measurements

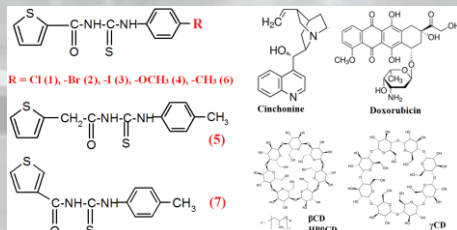
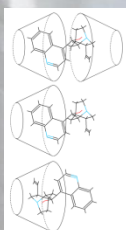
## Methods

All records of UV-Vis spectra were carried out on a Carry 300 Bio spectrophotometer equipped with a temperature controlled cell holder in the range of 200 – 600 nm using 1x1x4 - cm micro quartz cells with teflon stopper. The stoichiometry of the inclusion complexes was assessed by continuous variation method (Job's method) by varying the mole fraction of each component ( $R = [\text{host}] / ([\text{guest}] + [\text{host}])$  from 0 to 1 and the total molar concentration of the species is kept constant. The difference in absorbance ( $\Delta A$ ) measured at proper wavelength (nm) between solutions containing only guest and the guest host mixtures, multiplied by the molar ratio of [guest] was plotted as a function of the  $R$  of [guest]. The stoichiometric ratio of the inclusion complex is corresponding to the point where the derivative of the curve is zero. The absorption spectra were recorded at 25°C. DSC curves were recorded on a power compensated differential scanning microcalorimeter (Perkin Elmer 8500), under a heating rate of 10 °C/min in nitrogen flux. The apparatus was calibrated for temperature and enthalpy by melting high purity indium. The thermal curves were recorded using aluminium pans with crimped lids and the registered data were processed with Pyris Software for Windows. Also, DSC measurements were done using a TG analyzer coupled with DSC (Setaram Setsys Evolution 17) in open alumina crucibles of 100  $\mu$ L. The calorimeter was calibrated using recommended standards of indium ( $\Delta H_{\text{fus}} = 28.46 \text{ J g}^{-1}$ ). The samples masses have been between 1 and 2 mg. The measurements were performed at a heating rate of 10 °C/min in flowing argon atmosphere (16 mL min<sup>-1</sup>).



1:1 binding models and  
1:2 nanocapsule of CDs  
with cinchonine

## Materials



## Preparation of samples

The solid state complexes were prepared in 1:1 and 2:1 molar ratio of the host and guest. The pure active drug was dissolved in 50% (v/v) ethanol solution then the solution was added dropwise into a volume of cyclodextrin solution. The mixture solution in corresponding molar ratio was stirred and incubated at 25°C then the obtained product was dried into an oven at standard temperature for 24h. The resulted solid compound was used for investigations.

The liquid solutions used in UV-Vis and DLS analyses were also prepared in 50% (v/v) ethanol solution.

## Conclusions

- It was observed that depending on the relative sizes of the cyclodextrin and the guest molecule, more than one guest can be accommodated inside a single cyclodextrin cavity.
- If the guest molecule is long enough (the case of the 2-thiophenecarboxylic acid thioureas drugs), there is the possibility of 2:1 host:guest complex formation.
- In case of the Dox/ $\gamma$ CD system, the nanocapsule formation is found to be highly sensitive to the concentration of the Dox molecules.
- The drug Cinc is also able to form sandwich-type inclusion complexes with cyclodextrins.

## References

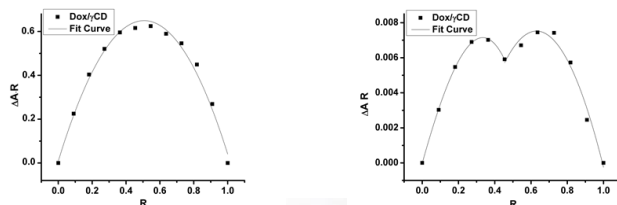
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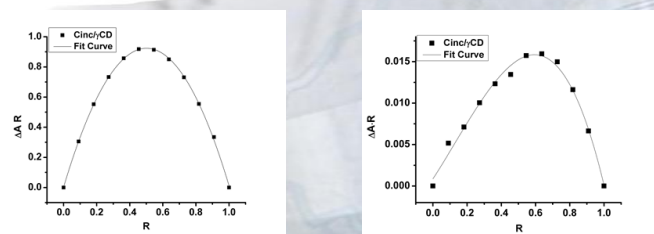
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## Experimental results

### Stoichiometry of the complexes caused by concentration variations

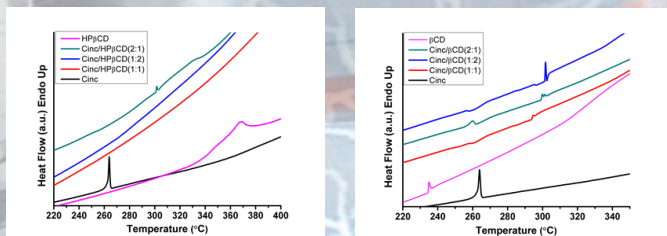


The Job's plot of Dox/ $\gamma$ CD complex system at concentration of  $10^{-5}$  M (the left side plot) and  $10^{-3}$  M (the right side plot)

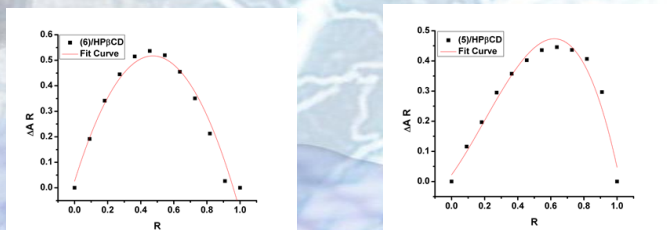


The Job's plot of Cinc/ $\gamma$ CD complex system at concentration of  $10^{-4}$  M (the left side plot) and  $10^{-3}$  M (the right side plot)

### The DSC curves of different Cinc: host molar ratios - The influence of the presence of native and functionalized CD

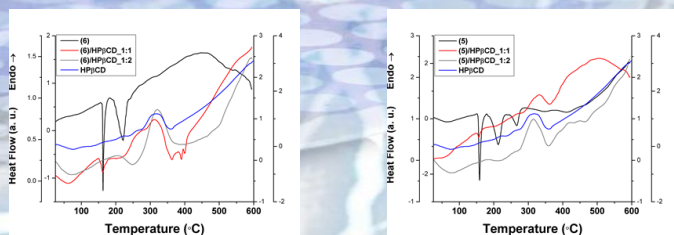


### Stoichiometry variation caused by guest length



The Job's plot of (5)/HP $\beta$ CD (the left side plot) and (6)/HP $\beta$ CD (the right side plot) systems at concentration of  $10^{-5}$  M

### The DSC curves of different guest:HPβCD molar ratios - The influence of the guest length



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