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Ɓenzocaine Schiff base-β-cyclodextrin inclusion complex

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Abstract:
Schiff base was prepared from the condensation of benzocaine and o- vanillin and then formulated as inclusion complexe with β-cyclodextrin.The mode of interaction was confirmed by spectroscopic methods. An increase of Schiff base solubility was observed in phase solubility studies. The results obtained from SEM proved the formation of inclusion complex. The partical size increase with increasing β-CD concentration with decrease the negative value of Zeta potential.

Keyword: *Benzocaine ,Schiff base, inclusion complex, phase solubility, SEM, zeta potential .*

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I. Introduction

Benzocaine an ester has been used for relief of local pain(1).Schiff base is nitrogen analogue of an aldehyde or ketone(2). Some of these Schiff bases show antibacterial(3),antifungal (4)and antiviral(5) activates .An inclusion complexes is a system consist of a certain chemical compounds has a cavity that widens to another compound(guest) via van der walls forces and not via covalent bonds(6). Cyclodextrins are well established hosts for the formation of inclusion complexes with many drugs to improve many important properties such as enhancement the solubility of poorly soluble drugs, to control the release, increase the aqueous stability of drug against photo and thermal degradation. etc(7-9). There are several method that are used in preparation the inclusion complexes all of them are a physical mixing in which no chemical reaction occurs between the guest and host, the most common methods are,Freez drying, kneading, spray drying,coprecptation etc.(10).

II. Material and Methods

Material: All solvents employed in synthesis were of extra pure, Benzocaine were obtained from ChemCenter ,o-vanillin were obtained from Merk,and β-CD were obtained from Across Organic .

Instruments:

IR spectra were recorded on a Shimadzu ,FT-IR-Spectrophotometer as a KBr disk .HNMR spectra were recorded on Bruker 500(500MHz),DMSO-d6 was used as solvent and TMS as internal reference. The mass spectrum of the Schiff base was recorded by EI-70eV with an Agilent Technology 597SC, morphological structure of Schiff base and there inclusion complexes were photographical using Scanning Electron Microscopy. Photographs were taken with excitation voltage 20kv and magnification factor of 2.5kx. Partical size distribution of sample were investigated .

Synthesis of ethyl 4-((2-hydroxy-3-methoxybenzylidene)amino)benzoate:

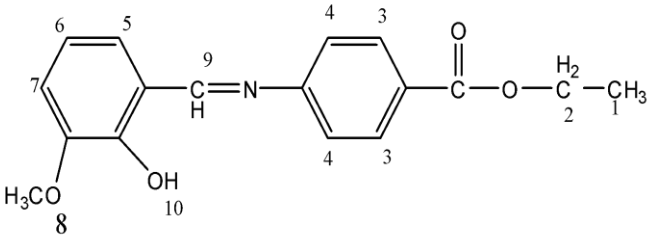
The titled Schiff base was prepared by reflexing an equimolar of benzocaine and o-vanillin in 50 ml absolute ethanol for ~ 5hrs. The resulting orange precipitate which obtain during the reaction filtered hot and washed with cold ethanol, dried in air, m.p101-103C° yield 70%.

Preparation of Schiff base-β-CD inclusion complex:

The freeze-drying method was employed to prepare the inclusion complex as following an equimolar of Schiff base and β-CD were mixed in 50 ml deionized water and the mixture was stirred at room temperature for 3 days, than the solution was freezing and lyophilized in a freeze drying type (CHRIST, model alpha1-2LD plus, Germany). The resulting fine powder was collected and kept in a desicator over silica gel.

III. Results and Discussion

The prepared Schiff base in this study is stable, springly soluble in common organic solvent and very soluble in DMF and DMSO and confirmed by spectroscopic methods where the mass spectrum (Fig:1) shows the molecular ion (M+▪) at m/z 299 which exactly equal the molecular weight of the proposed structure



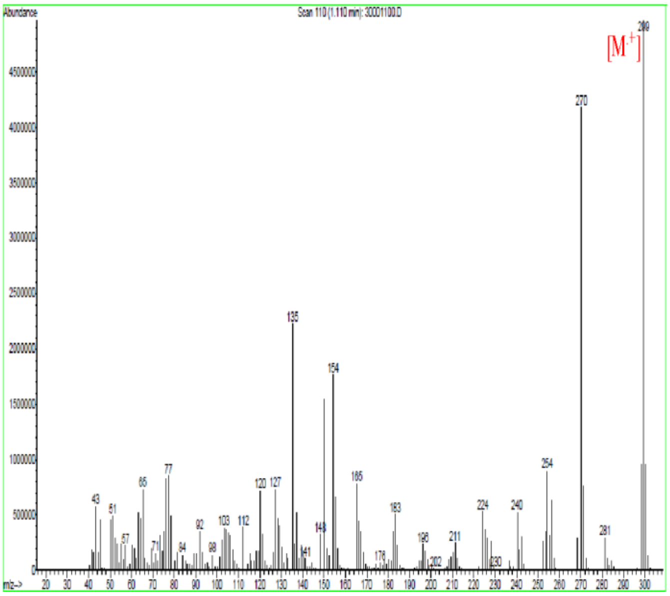


Fig.1:mass spectrum of Schiff base.

The IR spectrum of Schiff base :

(Fig.2) show the following bands, very strong band at υ1707cm-1 attributed to stretching vibration of carbonyl group, medium band at υ1647cm-1 attributed to C=N stretching which indicate the condensation of aldehyde with amine , strong to medium bands at the region 1575-1462cm-1 attributed to skeletal C=C, strong band at υ1367cm-1 (C-N), strong band at υ1278 cm-1 for phenolic C-O and another strong band at υ1199cm-1for C-O-C.

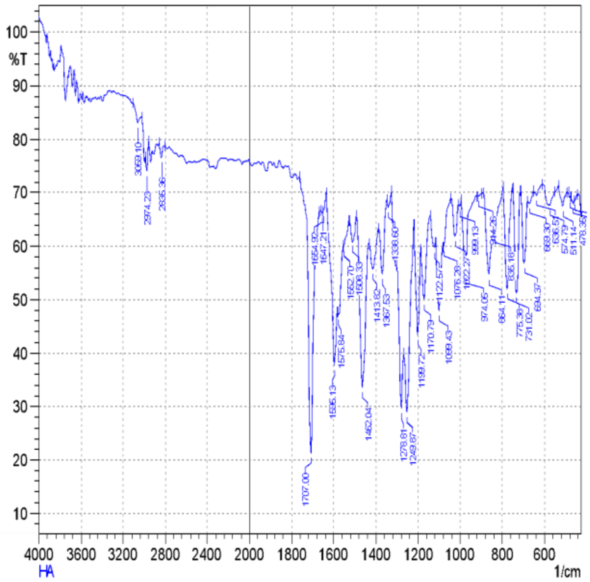


Fig.2:IR spectrum of Schiff base

The HNMR spectrum of Schiff base :

(Fig.3) show the following signals The signal at δ8.9 ppm which confirm the presence of azomethane proton (HC=N) , a triplet signal δ1.3333ppm, and a quartet signal at δ4.3306ppm (J=7.1Hz) which attributed to CH_3CH_2- group, a singlet signal at δ3.83ppm attributed to methoxy protons, the aromatic protons appear at the region δ6.92-8.036ppm . The down field signal at δ12.7354 ppm attributed to OH proton

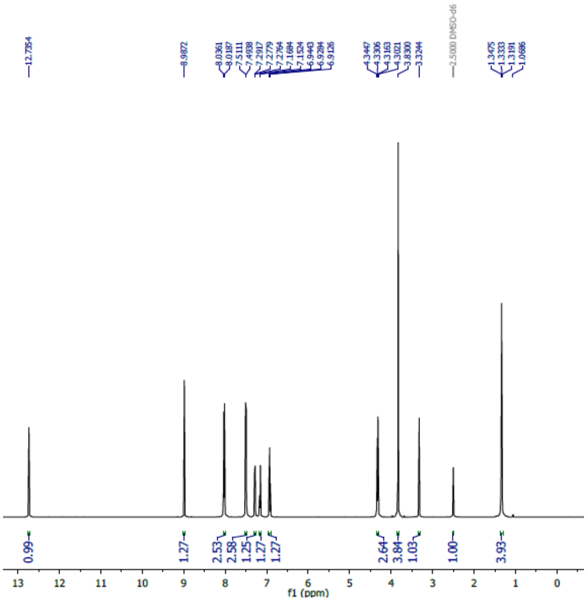


Fig.3:HNMR spectrum of Schiff base

FT-IR of inclusion complex :

The IR spectrum of inclusion complex (Fig.4) give evident to complex formation between Schiff and β-cyclodextrin where the bands shifts and decrease or increase in intensity when compared the result between the IR spectrum with that of free Schiff base and free β-CD. The band at 2931cm-1 which attributed to C-H stretching vibration in free β-CD appear at 2927cm-1 (Δυ= - 4cm-1) in complex spectrum, also a very broad band was observed at 3360cm-1 which characteristic to β-CD inclusion complexes. The strong band at 1707cm-1 in free Schiff base spectrum shifted to high frequency (Δυ= +5cm-1) and decrease in intensity, all bands attributed to benzene ring decrease in intensities in inclusion complex spectrum due to the host- guest interactions.

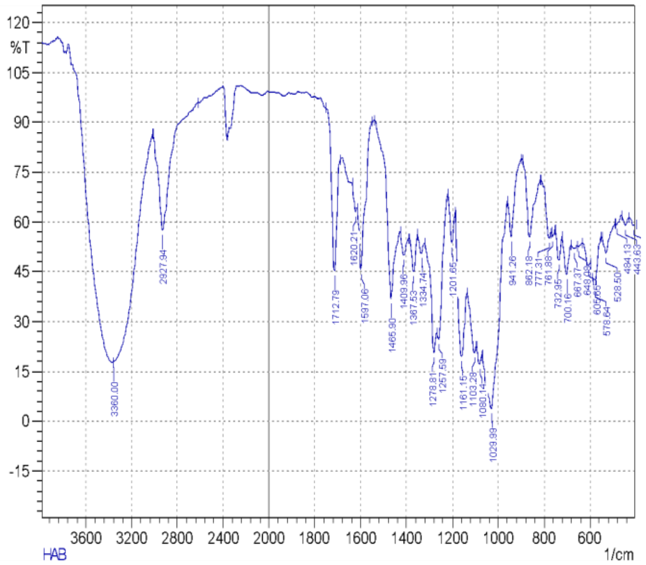


Fig.4:IR spectrum of inclusion complex

HNMR of inclusion complex:

A comparison of HNMR spectrum with free Schiff base (Fig.3) in the aliphatic region both the signals attributed to protons of cyclodextrin and hydroxyl protons were appear with small change in chemical shift but H3 and H5 which located in the cavity shifted to high field (Δυ= -0.06 ppm) for H3 and (Δυ = -0.13ppm) for H5,asignfication change in chemical shift of a signal of CH3 andCH2 protons of the guest where observed where the methyl protons shifted to and CH2 protons shifted to, also the aromatic protons of the guest show a significate change in intensity and chemical shifted where the all protons shifted downfield as depicted in the (Fig.5, Fig6).

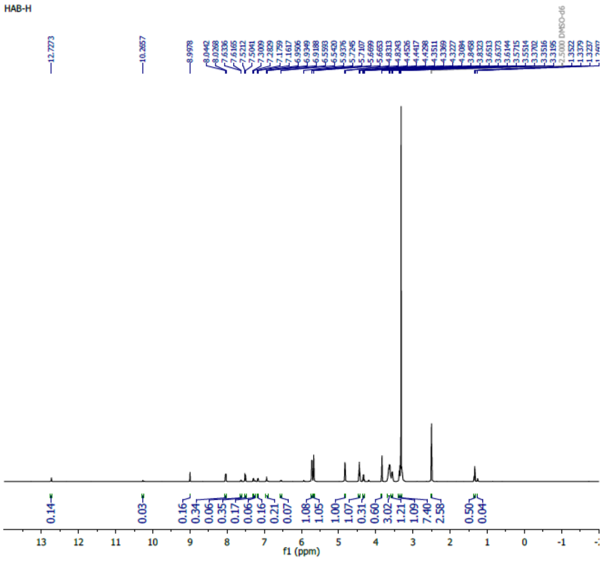


Fig.5:HNMR of inclusion complex

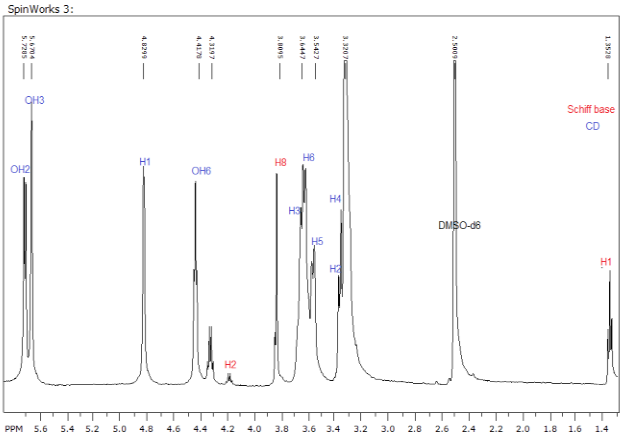
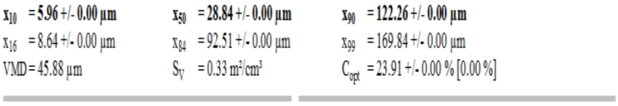


Fig.6:HNMR spectrum of inclusion complex for aliphatic region

particle size distribution:

DLS technique was employed to measure the size distribution of inclusion complex (Fig.7). The obtained result for a suspension of the inclusion complex in water. The PSD curve presenting 10%(d0.1) of particle with diameter less than 5.96 µm and 90%(d0.9) less than 122.26 µm and the surface volume SV equal o.33m2/cm3.



x_{10} = **5.96 +/- 0.00 µm**
x_{16} = 8.64 +/- 0.00 µm
VMD = 45.88 µm

x_{50} = **28.84 +/- 0.00 µm**
x_{84} = 92.51 +/- 0.00 µm
S_V = 0.33 m^2/cm^3

x_{90} = **122.26 +/- 0.00 µm**
x_{99} = 169.84 +/- 0.00 µm
C_{opt} = 23.91 +/- 0.00 % [0.00 %]

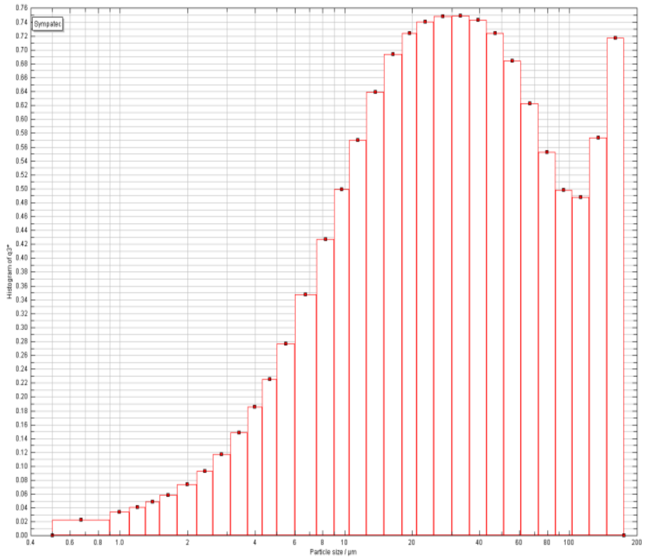


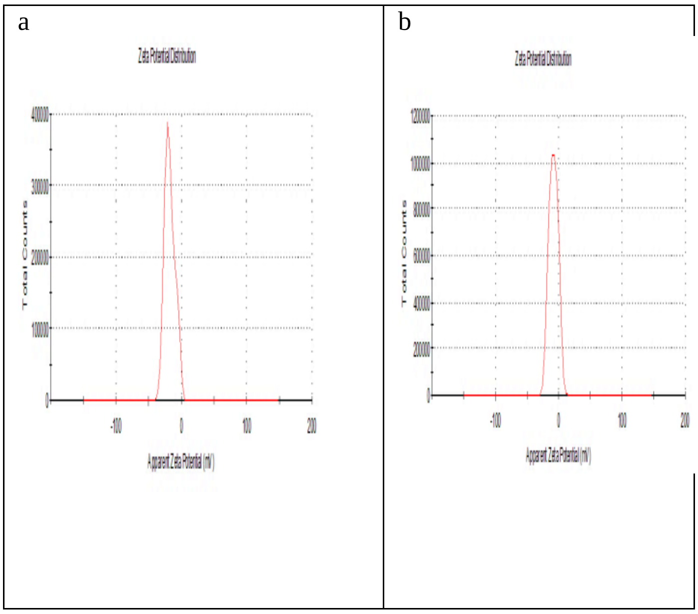
Fig.7:practical size distribution of inclusion complex.

Zeta potential:

A colloidal solubility of the inclusion complex dispersed

In water was examined by measurement the zeta potential together with the hydrodynamic size of free Schiff base in deionized water and in solution of β-CD in concentration of 0.001,0.003 and 0.006(Fig.8).

The free Schiff base distribution profile showing one distribution curve around 110 nm with polydispersity index equal 0.261nm,while the inclusion complex from the addition of free Schiff base in different concentration of β-CD displayed different size distribution curves ,all of them show two distribution curves the less intense one in the range 39-82nm and another intense curves in the range >100nm and the PDI increase with increase of β-CD concentration as shown in (Fig.8),the results can be explained by the fact that Schiff base interact in solution with the β-CD ,and the increase the polydesprive of mixture with increase the β-CD concentration compared with the free Schiff base in deionized water indicate that the mixture are more hetrogence .



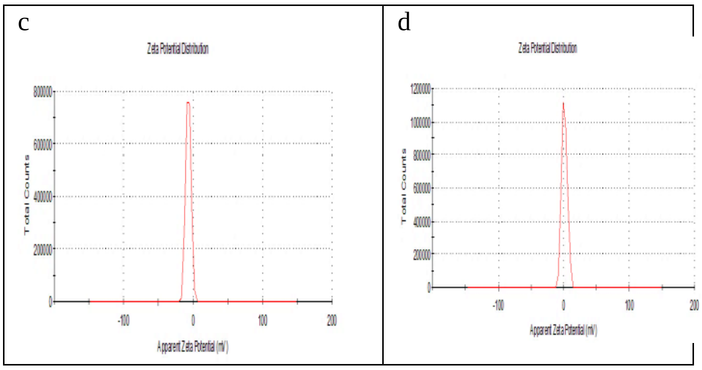


Fig.8: Zeta potential of Schiff base

Phase solubility:

The phase solubility were carried out following Higuchi and Connors method, first the UV-visible spectrum of pure Schiff base was recorded in deionized water, to determine λmax the result obtained from spectrum (Fig.9) show a λ at 271.4nm which attributed to π- π* transition (ϵmax=9800 L.mol-1.cm-1) and another weak band at 343nm,(ϵ=300) which attributed to n- π*. The second step in the preparation of asolution containing excess of Schiff base in a 25 ml of β-CD concetrations ranging from 0.001 to 0.015M. The volumetric flask were stirred for 24h at room temperature and then filtered and the concentration of Schiff base was plotted against concentration of β-SCD(fig.10) .

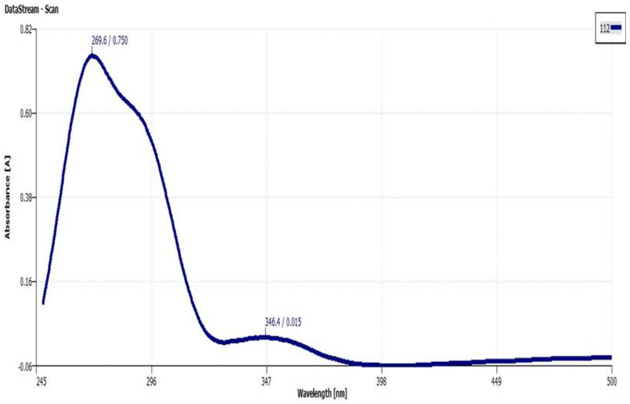


Fig.9: the UV-visible spectrum of pure Schiff base.

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The stability constant was calculated from the relation :

$$K_{1:1} = \frac{\text{slope}}{S^{\circ}\ (1\text{-slope})}$$

Where S_0 is the intrinsic solubility of Schiff base from the (Fig.10) it can be seen that the solubility increase with increase the concentration of β-CD solution and the resulted graph classified as AL type.

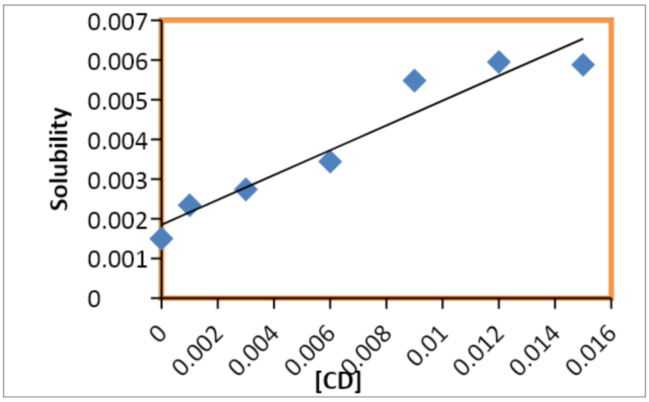

Fig.10: Phase solubility of Schiff base.

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