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Schiff base-β-Cyclodextrin Inclusion complexe

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ABSTRACT: A novel inclusionComplex of Ethyl 4-((4-hydroxybenzylidene)amino)benzoate(HB) with B-CD was prepared by freeze- drying method. The mode of interaction between Schiff base and β-CD has been studied by IR 1HNMR and SEM methodsZeta potential of both Schiff base and the complex were recorded and the results showed high negative value which indicate the possibility of formulated this complex as a suspension or emulsion for long time .The phase solubility studies in water was studies using Higuchi and Connors method, the result showed that The Schiff base with β-CD forming a complex with stability constant of 775.69 M-1 which indicated the formation 1:1 molar ratio complex , and the solubility enhanced by 5 Fold.

Keyword: Benzocaine,inclusion complex,zeta potential ,Higuchi ,Connors ,SEM .

I. INTRODUCTION:

The term inclusion complexes was introduced by schlenk in 1950(1), since this date many thousands of this type was prepared and study the effects of the interaction between guest and host especially in drugsindustries(2-5).No covalent bond is established between the guest and host but electrostatic attraction such as vander wallsforces,hydrogen boding are the driving forces to formation the complex(6) .The cyclodextrins that are most commonly studied are α,β and γ – cyclodextrine besides numerous derivatives of these compounds have also been studied .The encapsulation of guest molecules by taking up a whole molecule or some part of it into the hydrophobic cyclodextrins cavity will affect many of physicochemical properties such as enhancement the stability , solubility in water , sheif life of drugs etc.(7-10).

II. EXPERIMENTAL:

Materials : β-Cyclodextrin was purchased from Across organic company,p-hydroxybenzaldehyde and benzocaine from ChemCenter and they were used as given, Deionized water was used throughout the study , All solvents employed in synthesis were of pure.

Instrument :IR spectra wre recorded as KBr disks on a Shimadzu FT-IR-spectrophotometer .1HNMR spetra were recorded on Bruker 500 MHZ , The EI-mass spectrum of pure Schiff base was recorded with an Agilent Technology 5975C .Zeta potential of the susbendedpartical in deionzed water were determined after sonication for 20 min on Zetasizer type Horipa , phase solubility study were performed on a CE7200UV-visible spectrophotometer using 1cm quartz cell.

Preparation of Schiff base Ethyl 4-((4-hydroxybenzylidene)amino)benzoate(HB). 1.65g (10mmole) of benzocaine and 1.22g (10mmole) of p-hydroxybenzoaldehyd dissolved in 50 mL of absolute ethanol and the resulting solution was refluxed for ≈ 5 hrs, the reaction monitered by TLC (ethyl acetate: hexan ,1:2). The resulting solid yellow which optained during the process was separated and washed with cold ehanol and dried in air to give a yellow crystals m.p 160-161Coyield77%.

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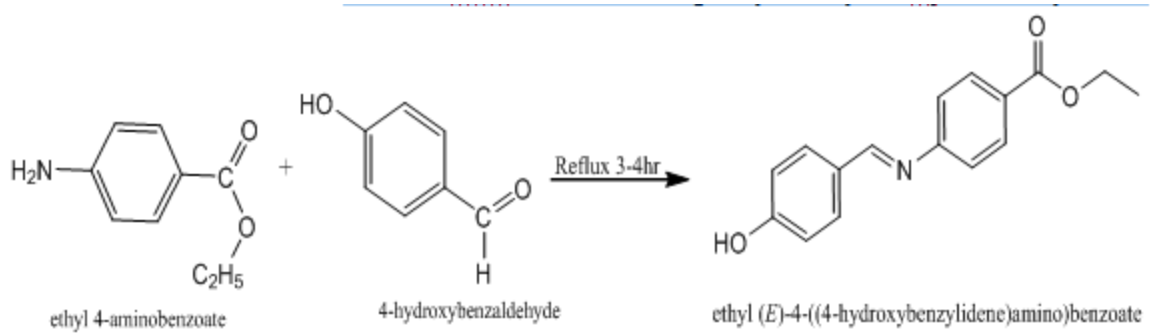

ethyl 4-aminobenzoate + 4-hydroxybenzaldehyde → ethyl (*E*)-4-((4-hydroxybenzylidene)amino)benzoate

Preparation of inclusion complexes:

The inclusion complex of Schiff base and β-CD was prepareted at a molar ratio 1:1 using freeze- drying method .Where the Schiff base and β-CD mixed in 50 mLdeionized water and stirr for 72 hrs at room temperature , and the freeze in refrigerator .The lyophilized in freeze dryer(CHRIST ,alpha -2LD) the resulting fine palle yellow powder was collected and kept in descator over silica gel .

III. RESULTS AND DISCUSSION:

Schiff base characterization : The formation of Schiff base was confirmed (by mass ,IR and 1HNMR) . The EI-massspectrum(Fig.1) show a molecular ion at m/z269 in 100 % intensity(base peak) which exactly equal to the molecular weight of the suggested structure .

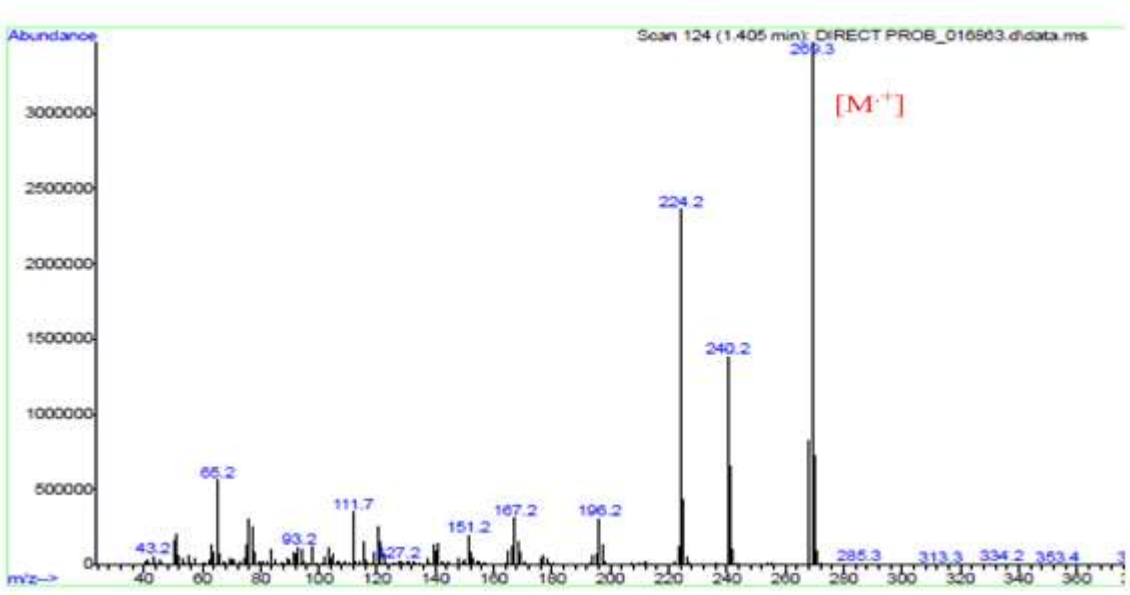

Fig.1: EI -mass spectrum of Schiff base.

The IR spectrum (Fig.2 a) show a very strong band at υ1720 cm-1 attributed to stretching vibration of C=N which indicate the formation of Schiff base ,also some strong bands at υ 1577.7,1512,1444 which attributed toC=C ,strong band at υ 1286.5 cm-1 attributed to C-N and another strong band at 1242 cm-1 attributed to streching vibration of C-O (11) .

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The1 HNMR spectrum (Fig. 3) show the flowing signal at δ 1.3 (t ,3H,CH3,J=7.05 Hz) ,at δ 4.3 ppm(q , CH2 ,J= 7.1) four doublet signals attributted to aromatic protons, at δ 6.89 ppm for protons No.6 (d ,2H,J=8.6 Hz) , at δ 7.8 ppm attributed for protons No.5 (d ,2H,J=8.6 Hz) , at δ 7.97ppm for protons No.3 (d ,2H,J=8.5 Hz) and at δ 7.27 ppm for protons No.4 (d ,2H,J=8.5 Hz).

The singlet signal at δ 8.478 ppm attrubted to azomethane proton (12) ,and the singlet signal at δ 10.22 ppm attrubted to OH proton.

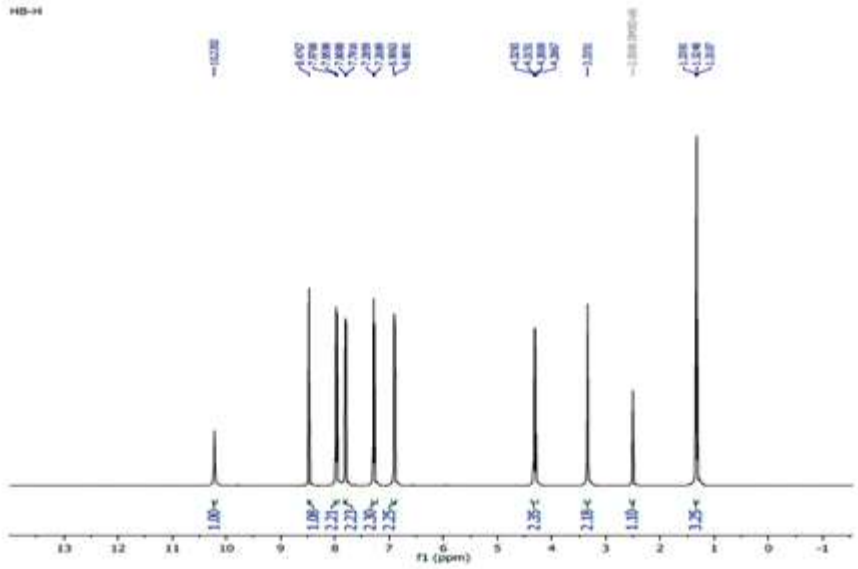

Fig.2: :HNMR spectrum of Schiff base

Characterization of inclusion complexe:

The FT-IR spectrum of Schiff base / β-CD(Fig .4)wase compared with FT-IR of Schiff base , most bands of free Schiff base at 1720, 1577,1286,1166 which attributed to C=O ,C=C, C-N and C-O respectively are show significant change in position and intensity which indicate the strong interaction of whole Schiff base with C-C,C-O or O-H group of cyclodextrines.

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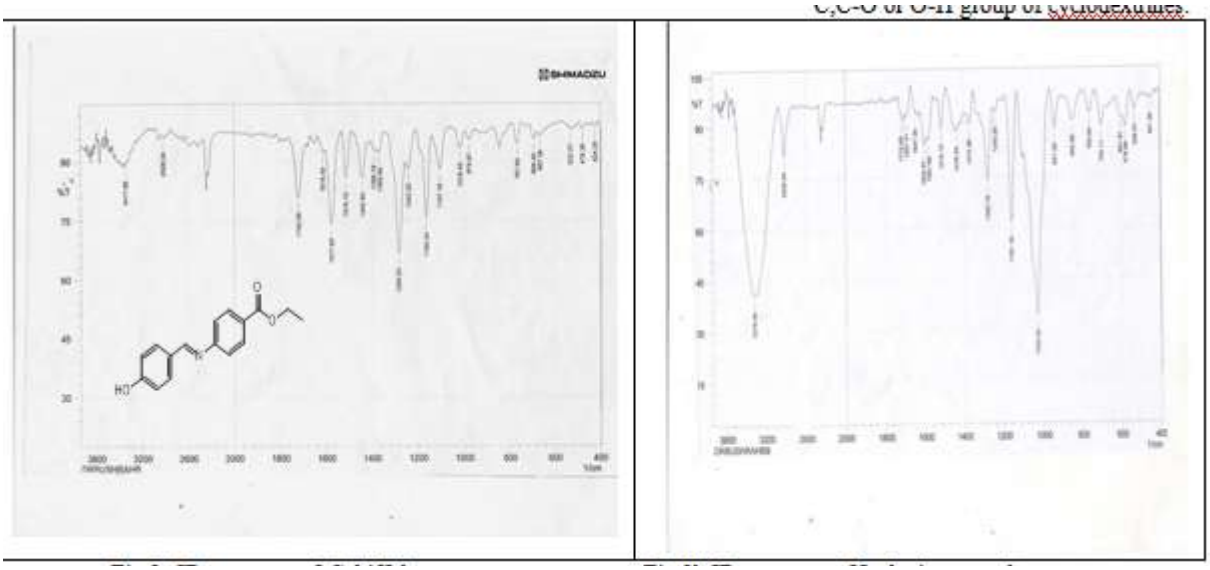

Fig.3a:IR spectrum of Schiff base

Fig.3b:IR spectrum of Inclusion complex

Acomparison of 1HNMR spectrum of the inclusion complex with 1HNMR spectrum of freeSchiff base a significant change in the position of most signals were observed ,the H3 and H5 protons of cyclodetrine shifted to high field Δδ =-0.225 ppm for H3 and -0.2296 ppm for H5. The signals of CH3 ,CH2 , azomethine proton, OH proton , and all aromatic protons were shafted to high field which indicated the interaction of base molecule withCD cavity (13) .(Fig.4a,4b)

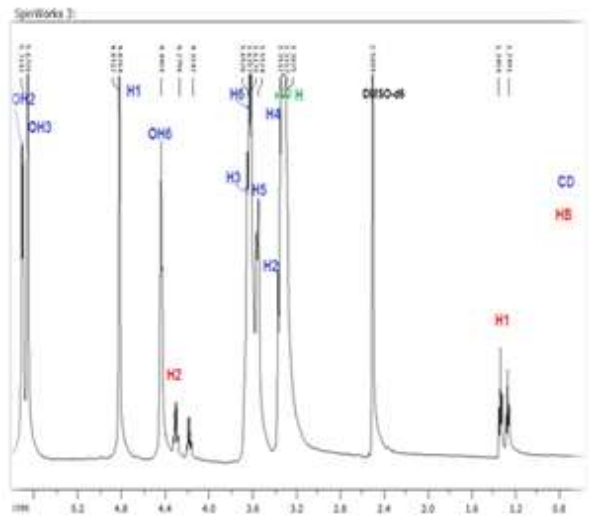

Fig.4a:HNMR spectrum of inclusion complexe in aliphatic in aromaticregion .

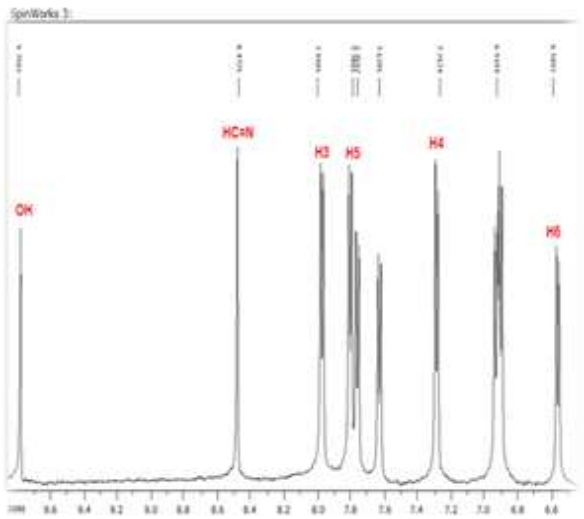

Fig.4a:HNMR spectrum of inclusion complexe region.

Zeta potential : Zetapotential or double layer potential of free Schiff base and their β-CD inclusion complex were measured after dispersion each one in water and soniciated for 20 min .The results indicated that the ZP of free Schiff base and inclusion complex equal -74.1 and -57.4 mV respectively which indicated that both Schiff base and their inclusion complex can be formulated as a colloidal solution stable for long time(14), The negative values of ZP may be attributed to OH groups (Fig.5a,5b).

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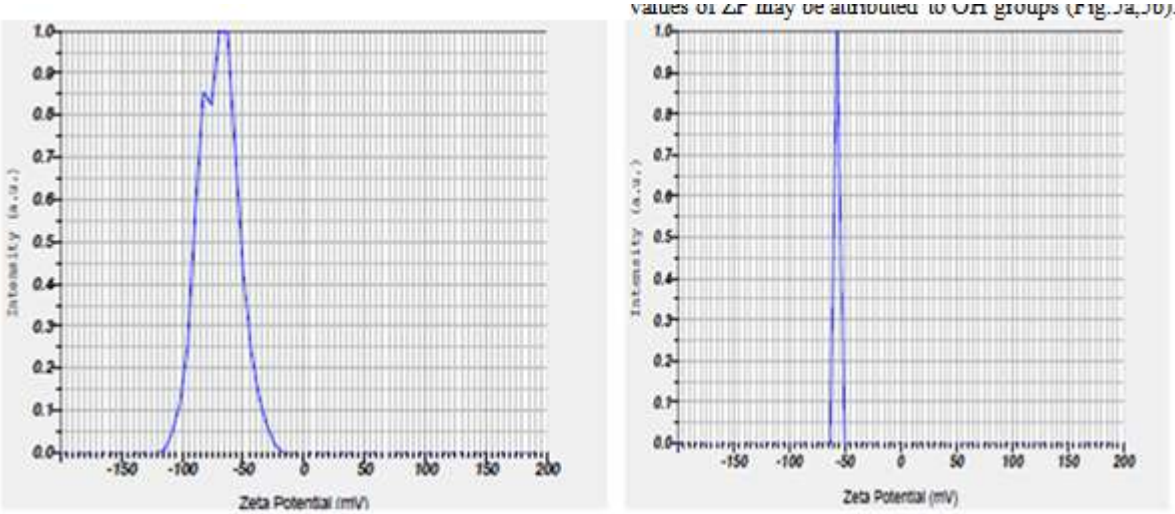

Fig.5a: Zeta potential of inSchiff baseFig.5b: Zeta potential ofinclusion complex in a deionized water a deionized water

SEM : The results indicated that the Schiff base photographs showed a sheet like containing slits while the inclusion complex showed a plate like particlesand seems to be related to one component (inclusion complex) which indicated the totally encapsulated between guest and host(15).

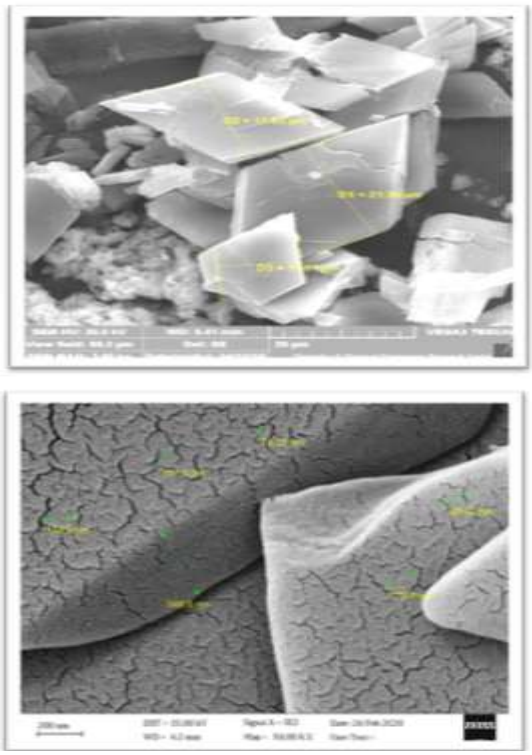

Fig.6a: Scanning electron microscopy (SEM) of Schiff base
Fig.6b: Scanning electron microscopy (SEM) of inclusion complex

Phase solubility:

The UV-visible spectrum(Fig.9) show absorption band at λ 285 nm(ε=12700 L.mol-1.cm-1) which attributed toπ-π* transition. Small shift (≈ 1nm) are observed in the UV spectra of Schiff base in different β-CD concentration , the increase in the absorption without change in the λ maxhave

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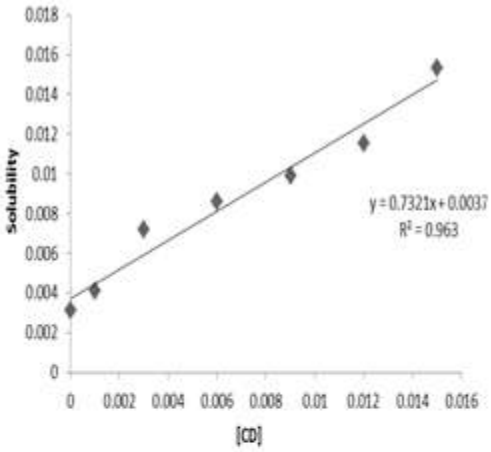
been considered as evidence for interaction between guest and host(16,17).

Phase solubility was carried out following Higuchi and Connors method(18) . The result show the solubility in water increase with β-CD concentration (Fig.10) where the the solubility increase by, ≈ 5 folds, the resulted graph classified as AL-type , and the stability constant was calculated using the relation.

Where so is the intense solubility of Schiff base .The value of K was found to be 882 M-1, and this result indicated the formation of the inclusion complexe as 1:1 (guest:host) where the literatures indicate that the values of K for 1:1 complex ranged from 50-2000 M-1, the high value of K means the strong iteraction(8) .



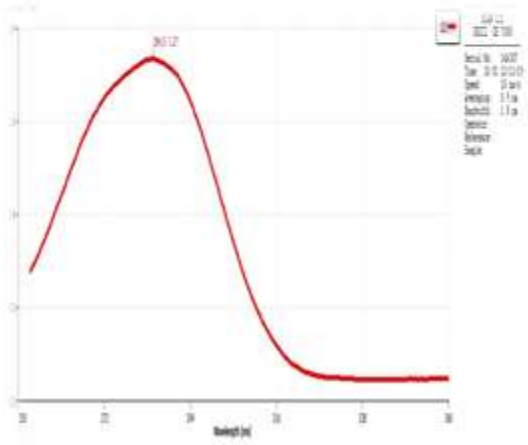


Fig.9:Uv spectrum of Schiff base(0.0001M)Fig.10:Solubility curve

REFERENCES:

[1]. Hermann Schlenk and DonaldM.Sand:The association of α and β-cyclodextrins with organic acid:J.Am.chem.soc.83(10)pp2312-2320-(1963).

[2]. S.Saha ,A.Roy and M.Nath Ray:Mechanistic Investigation of inclusionComplexes of a sulfa drug with α and β-cyclodextrine ,Ind.Eng.Chem.Res.56,41 ,pp11672-11683 (2017).

[3]. A.Kapor ,V.Nikolic and D.Ilic, Inclusion Complexes of amlodipine besylate and cyclodextrins , Central European of chemistry ,8,pp 834-841 (2010).

[4]. M .D .Octavia ,A.Halim and E.Zaini; Preoaration of simvastatin-β-cyclodextrine Complexes using Co-evaporation technique;J of pharmaceutical and Res .vol.7(2), pp740-747 (2015).

[5]. P.Sackhain ,C .Muankaew ,P . Jansook and T.Loftsson :Solubility of cyclodextrins and

Drug/ cyclodextrin complexes molecules ,23 ,pp1161(2018)

[6]. Jozsef Szejtli :Cyclodexteine Inclusion Complexes Chapter 2 pp79-185 (2020),Springer .

[7]. Pentewar R.S , Kshirsager N.,Sayyed S.Ali and Kulkarni K . :Formation of azithromycin and chloroquine phosphate FDT by enhancing their solubility using cyclodextrins complexes ,Der PharmaSinica 6(12) pp1-2 (2015) 8- BenjormasCheirslip , and JarupornRakmal: Inclusion complex formation of cyclodextrin with its guest and theirapplications,BioEng Med(2016) doi:10.15761/BEM.1000/08.

[8]. Choudhury S . ,Mitra AK. ,Kinetics of aspirin hydrolysis and stabilization in the presence of 2- hydroxyl propyle cyclodextrin:Pharm.Res 10, pp 156-159(1993).

[9]. Zaha .Mr . ,Wang Ls. , Liu Hwetal :preparation ,physicochemical characterization and in vetro dissolution studies of azithromycinecyclodetrine inclusion complexes:J .Inclphenomiu acrocycichem 85,pp 137 -149(2016) .

[10]. Larkin.P.:Infrared and Raman spectroscopy: Principles and Spectral Interpretation.Ia,ed.Elsevier:Amsterdam,(20 10).

[11]. H.Ebrahimi ,J .S .Hadi and H .S .AL-Ansari :A new series of Schiff base derived from sulfa drugs and indole -3- carboxaldehyde . Synthesis characterization ,spectral and DFT computational studies,Vol.1039 ,8 May 2013 pages 37-45.

[12]. Bouchemela H. , Mahdi F and Nouri L. :DFT investigation of host –guest intractions between α- Terpinol and β-cyclodextrin : J . InclphenomMacrocyclechem 95 ,247 -258 (2019) .

[13]. Robert J . Hunter :Zeta potential in colloid science 1st Edition,Elsevier (1988) .

[14]. Ficarra R . ,Ficarra P . , D . Bella MR , Raneri D . , Tommasini S. , Calabro ML , Gamberini MC and Rustichlli C : Study of beta- blockers /beta –cyclodetrins inclusion complex by NMR,DSC,X-ray and SEM investigation :J .of pharmaceutical and Biomedical Analysis 23(1) pp33-40 (2000) .

[15]. Ramnik Singh,NitinBharti .JxotsanaMadan and S.N.Hire math :Characterization of cyclodextrin inclusion complexes –A Review :Journal of pharmaceutical science and Technology. Vol.2(3),pp171-183(2010).

[16]. K .Uekama ,S .Narisawa , F .Hirayama and A.Otagiri. Improvement of dissolution and absorption characterist o benzodiazepines by CyclodextrinComplexation: Int .J .pharm .16(3),pp 327 -332(1983) .

[17]. Higuchi T. and Connors KA. :Phase solubility techniques ; Adv .Anal .Chem .Instrum ,4 ,pp 117 -212 ,(1965) .