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Preparation, and Evaluation of physical properties of Schiff base- β -Cyclodextrin inclusion Complexes

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ABSTRACT

Schiff base was prepared from the condensation of Sulfamethazine and N,N-dimethyl-4-aminobenzaldehyde, inclusion complex was formed using β -cyclodextrin to encapsulate it. The mode of interaction and characterization were studied using IR, HNMR and SEM. Aqueous solubility was studied through Higuchi and Connors method and the result shows the improvement of solubility by 3.5 folds and the complexes were formed in 1:1 molar ratio, the morphology of the particles was compared between Schiff base and their inclusion complexes and the result shows the change in the surface, shape, and size.

Keywords: Schiff base, cyclodextrin, complexes.

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INTRODUCTION

Schiff bases are the Compounds resulted from the Condensation of primary amines with carbonyl compounds to form an azomethine group (-C=N-) Schiff bases have a wide variety of applications in medicinal and pharmaceutical fields due to their biological activities. Schiff bases derived from Sulfa drug [1, 2, 3]. it is an important group of this type that has attracted the attention of many researchers.

Cyclodextrins are cyclic oligosaccharides with toroid conic shape Composed by 6, 7 or 8 (alpha, Beta and gamma Cyclodextrin respectively) glucose units linked by α -1, 4 glycosides bonds [4,5], Cyclodextrins especially beta type has been used to the formation of inclusion Complexes for many famous drugs. Where the Cyclodextrin and due the specific Structure behave as a host for many Lipophilic Compounds (guest) [6,7]. The importance of the formation of inclusion complexes between drugs and Cyclodextrins is to improve many physical properties such as enhancement the aqueous solubility of poorly soluble drugs, increase the thermal stability, Controlled the release of the drug, masking unwanted taste and unpleasant smell.

MATERIALS AND METHODS

Materials

β -cyclodextrine was purchased from across organic chemical Company, sulfamethazine was purchased from Sigma-Aldrich Co. All the Solvent used were of analytical grade.

Spectral measurement and instrumentation

Melting point was recorded on Thermo fisher apparatus. IR spectra were recorded as a KBr Pellets on Shimadzu FT-IR spectrophotometer in the rang 4000–400 cm^{-1} . ^1H NMR Spectra were recorded as DMSO- d_6 solution on a Bruker (500 MHz). EI-mass spectrum was recorded on Agilent Technologies type 5957C spectrometer. SEM images were performed using ZEISS SIGMA v from Carlzeiss Microscopy (Germany).

Methods

Synthesis of 4-((4-(dimethyl amino) benzylidene) amino)-N-(4,6-dimethylpyrimidin-2-yl)benzene sulfonamide

5mmole (1.39g) from sulfamethazine was dissolved in 15ml of hot absolute ethanol and 5mmole (0.745g) of N,N-dimethyl-4-aminobenzaldehyde dissolved in 15 ml of absolute ethanol was added drop wise, 2 drops of conc H_2SO_4 was added to the reaction mixture and the resulted solution was refluxed. The reaction monitored by TLC using (CHCl_3 : ethyl acetate) (6-4) as eluent. after the reaction Complete (~4 hrs), the mixture was Cooled and the precipitate filtered and washed by Cold ethanol and the orange Solid was recrystallized from ethyl acetate and the solid product 1.032g (yield 51%) m.p 217-219°C (Fig.1).

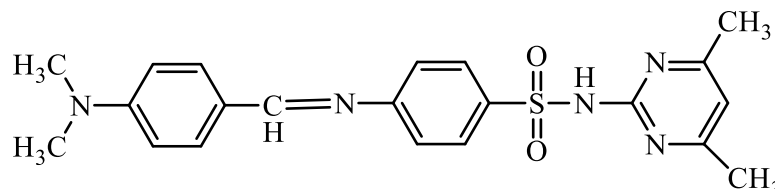


Figure 1: 4-((4-(dimethylamino)benzylidene)amino)-N-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide (N2)

Synthesis of inclusion complexes

Freeze drying method was employed to synthesis of inclusion Complexes. 1mmole of β -CD and 1mmole of N_2 was mixed in 50mL distilled water at room temperature and the remitted mixture was stirred for 72 hrs. Then the mixture lyophilized in a freeze dryer type CHRIST model alpha LD plus. The resulted fine Powder was kept in a desiccator over silica gel.

RESULTS AND DISCUSSION

FT-IR spectroscopy

The formation of Schiff base (Fig. 2) was confirmed by the appearance of characteristic strong band at ν 1608 cm^{-1} which attributed to azomethine group (HC=N-)[8]. The broad band at 3417 cm^{-1} attributed to N-H stretching vibration of sulfa moiety. The band at ν 1579 cm^{-1} attributed to C=N of sulfa moiety ring[9], another two strong bands at 1361 and 1161 cm^{-1} attributed to asymmetric and symmetric stretching vibration of O=S=O moiety [10,11]. The moderate band at ν 946 cm^{-1} attributed to S-N stretching Vibration[12] . The IR spectroscopy method gives good evidence of inclusion Complex formation between guest and Cyclodextrines where the shifted of the bands position and change of the intensities were observed when the guest molecule intrepid inside the cyclodextrines cavity. When Compared the IR spectrum of The inclusion Complex between the Schiff base and β -CD it can be seen that the very broad band centered at ν 3356 cm^{-1} which attributed to hydroxyl groups, these band appear in free β -CD spectrum at ν 3392 cm^{-1} .

Also a strong band appear at ν 2926 cm^{-1} attributed to C-H aliphatic. As significant change where observed in the position of azomethine group which shifted to lower frequency (-11.57 cm^{-1}) and decrease in the intensity which indicated the presence of the group inside the β -CD cavity [13-15]. also the other band related to Schiff base were shifted either to lower or higher frequency as shown in (Fig.2).

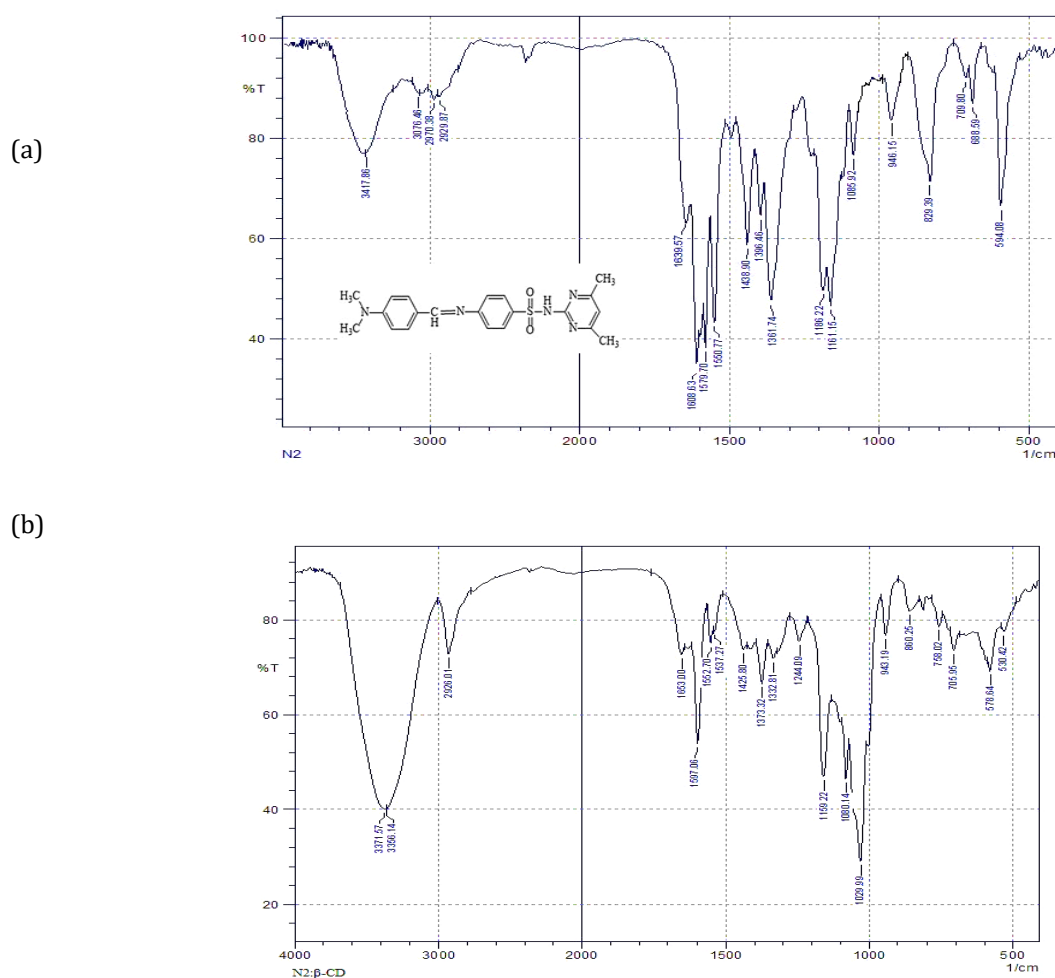


Figure 2: FT-IR spectra of (a) Schiff base(N2) ,(b) inclusion Complex (N2:β-CD)

El-mass spectrometry

The El-mass spectrum of Schiffbase (Fig3) show the molecular ion peak at $m/z = 409$ which indicate the condensation of sulfa with aldehyde in 1:1 molar ratio. The (scheme1) show the mode of fragmentation of some important fragments.

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 Acquired : 2 Jan 2007 3:52 using AcqMethod tast.M
 Instrument : MSD
 Sample Name: N2
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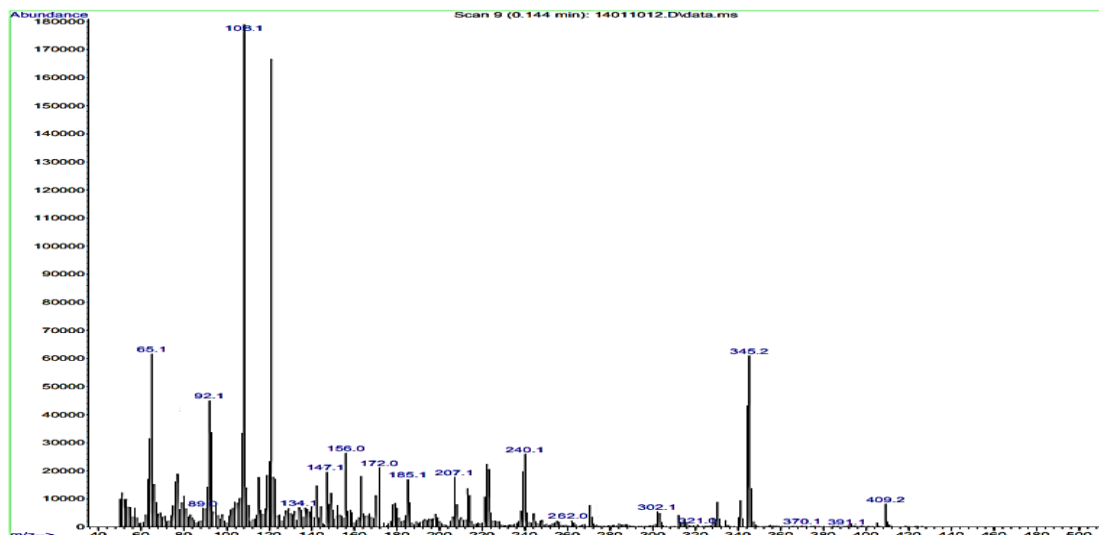
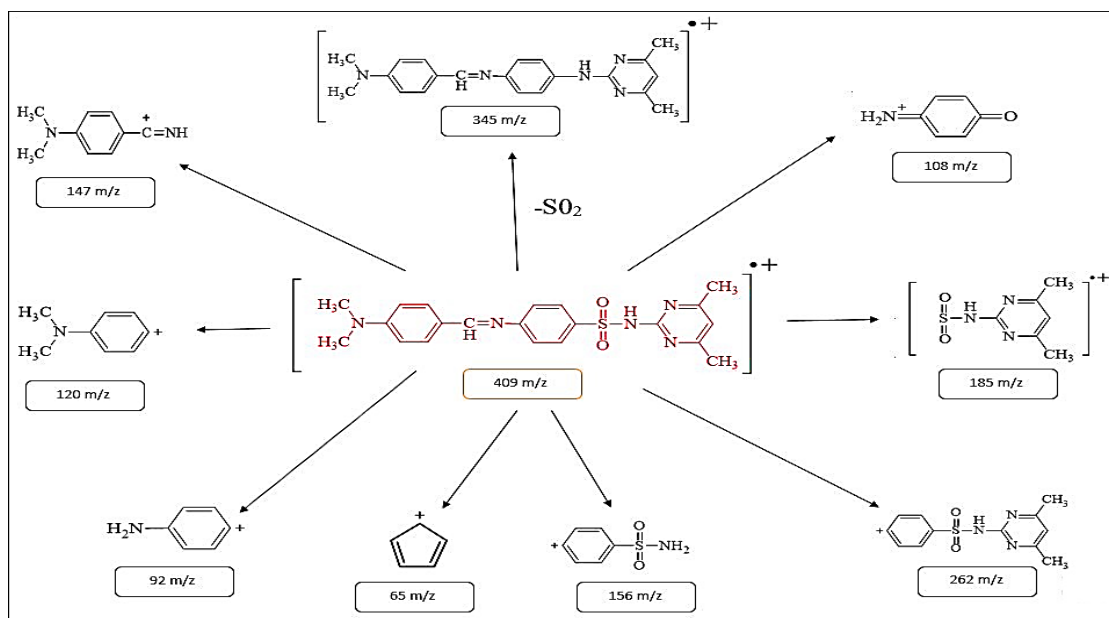


Figure 3: El-mass spectrum of Schiff base(N2)



Scheme 1: mode of fragmentation of Schiff base (N2)

¹HNMR Spectroscopic Studies

The formation of Schiff base was confirmed by the appearance of a signal attributed to azomethine(HC=N) proton at δ 8.09. ppm [16,17], the signal of methyl groups of sulfa moiety appear at δ 2.25 ppm while the methyl groups of aldehyde a moiety of appear at δ 2.97 ppm. The pure β -CD HNMR spectrum. Show the H3 and H5 protons which located inside the cavity at δ 3.60 and 3.53 ppm. respectively these signal shifted to higher field upon complexation with Schiff base molecule as shown in (Fig 4).The other signals of Schiff base were shifted and the results are tabulated in Table1.

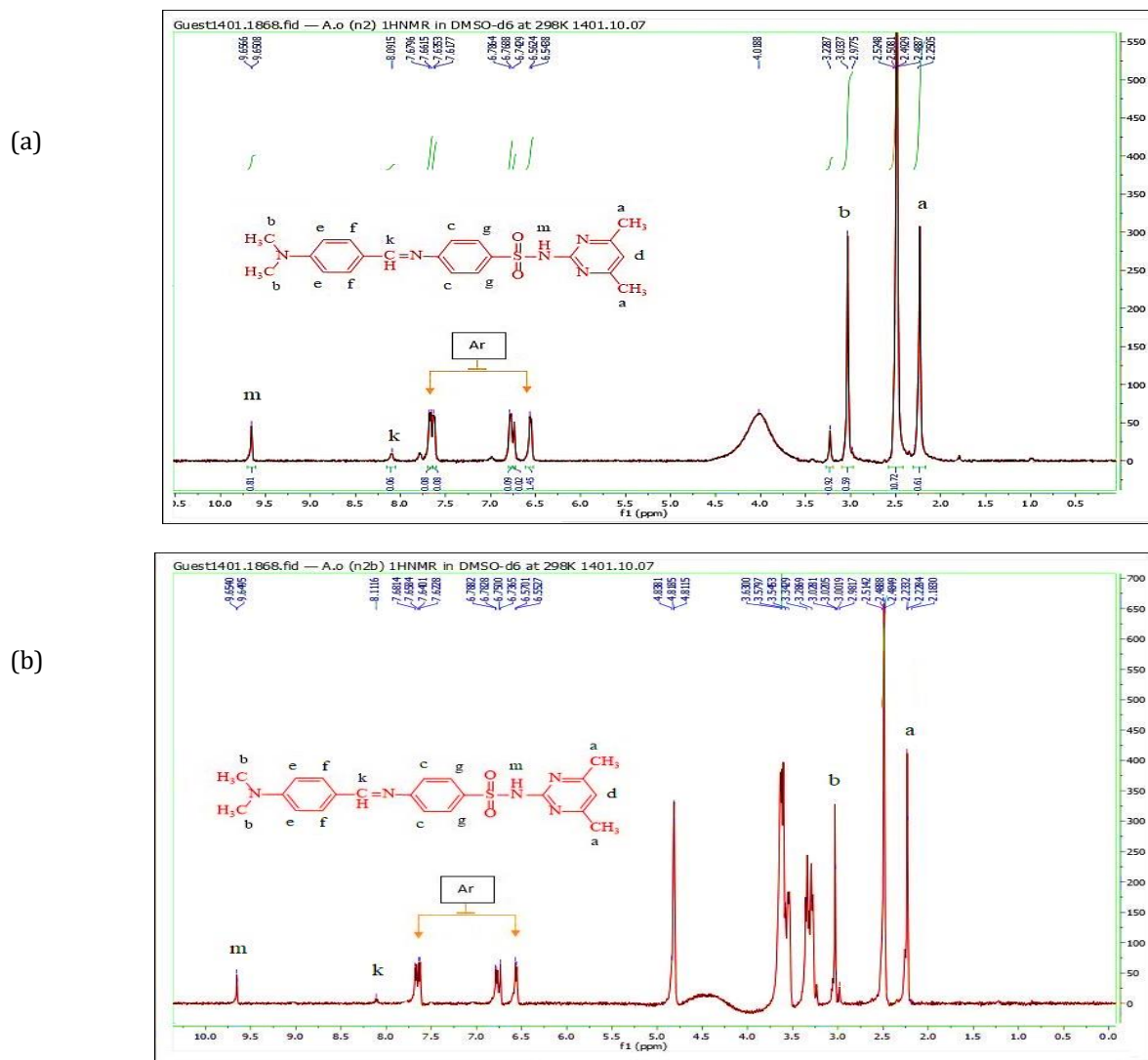
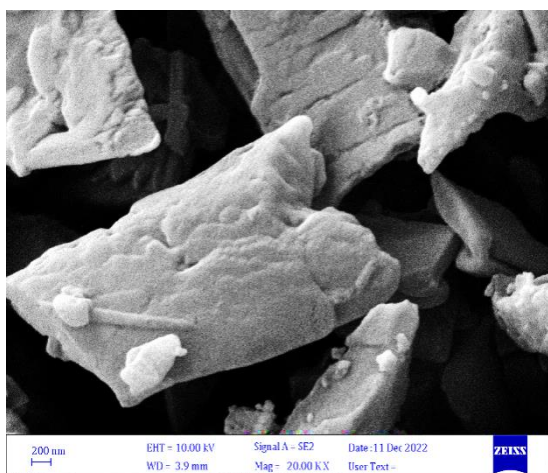
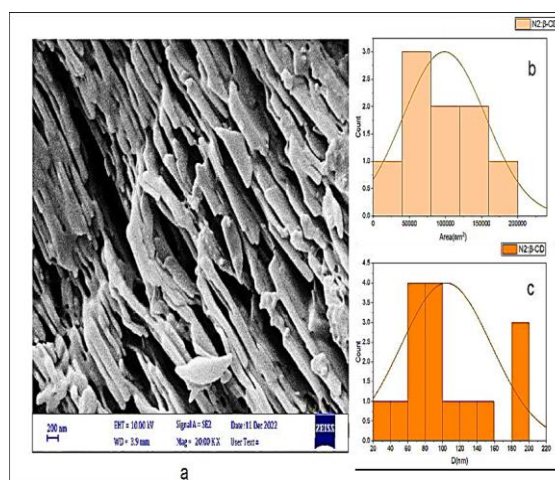


Figure 4: ¹HNMR spectra of (a) Schiff base(N2) ,(b) inclusion Complex(N2:β-CD)

Table1: ¹HNMR data of Schiff base and inclusion Complex

Substance	Proton	Free (δ) ppm	Complex (δ)ppm	$\Delta\delta$
N2	a	2.2505	2.1830	- 0.0675
	b	2.9775	2.9817	0.0042
	c	6.5438	6.5527	0.0089
	d	6.7429	6.7365	- 0.0064
	e	6.7688	6.7828	0.0140
	f	7.6177	7.6228	0.0051
	g	7.6615	7.6584	- 0.0031
	k	8.0915	8.1116	0.0201
	m	9.6508	9.6495	- 0.0013
β CD	H3	3.882	3.602	-0.280
	H5	3.754	3.535	-0.219

SEM: Results of SEM gives good evidence for formation of inclusion complex[19 ,18] by comparing the image differences between β -CD,Schiffbase and inclusion complex. (Fig.5) show the SEM image of Schiff base which appear as rock like and the inclusion complex image. (Fig.6) Show the Stick regular shape of rocks, also the increase of the surface area of inclusion complex was observed which estimated by origin image program.


Figure 5: SEM of Schiff base (N2)

Figure 6: SEM of N2:- β -CD Inclusion Complex

Phase Solubility study

The phase Solubility study of N2 in aqueous Solution was performed following Higuchi and Connor method[20] .excess of N2 was added to aqueous solution of β -CD in different concentration (0.001, 0.003, 0.009, 0.012 and 0.015 M.) The mixtures were shaking for 24 hr at room temp and then filtered.

The UV.Visible of N2 in water was measured as a 10^{-4} M to calculate the Molar absorptivity confident then UV-Visible of each solution was run (Fig7). The Phase solubility diagram for N2 with β -CD is shown in (Fig8)The result indicate the A_L type phaseSolubility and suggests the 1:1 molar ratio between N2 and β -CD were the K_c value (1514.24 M^{-1}) obtained using the formula [21,22]

$$Kc = \frac{\text{Slope}}{S_0(1 - \text{Slope})} Kc = \frac{0.8928}{0.0055(1 - 0.8928)}$$

and The Solubility enhance by 3.5 folds. The result are tabulated in(Figure8 and table2).

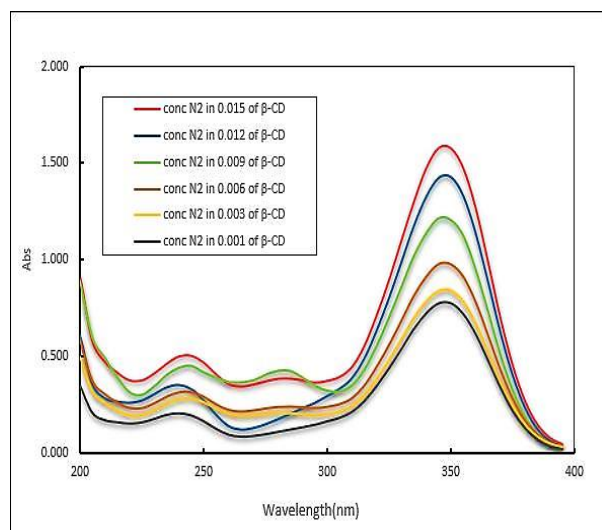


Figure 7: UV Spectra of N2 in different conc. of β -CD

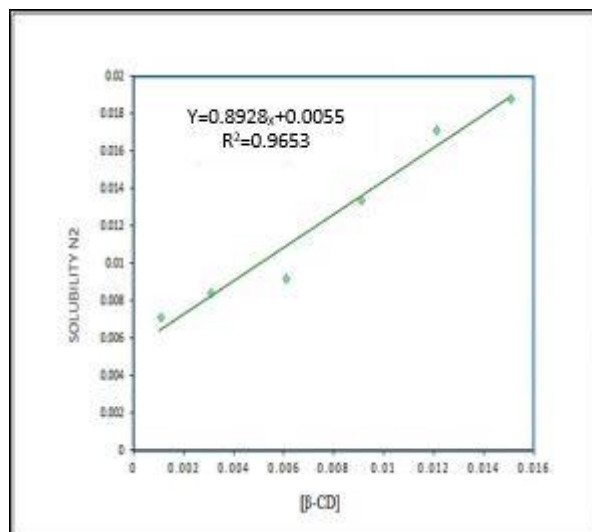


Figure 8: Phase solubility diagram of N2in β -CD

Table 2: phase solubility data of N2

[β -CD]	Solubility N2	[N2] g
0.000	0.0055	2.2495
0.001	0.0071	2.9039
0.003	0.0084	3.4356
0.006	0.0092	3.7628
0.009	0.0134	5.4806
0.012	0.0171	6.9939
0.015	0.0188	7.6892

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