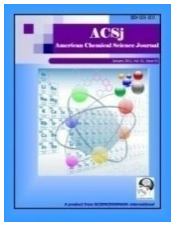

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Spectroscopic Study of Bifenox Complexation with α-, β- and γ-Cyclodextrin in Solution and Solid State

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Authors' contributions

This work was carried out in collaboration between all authors. Author AGAS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors PRG, PS and AGAS managed the analyses of the study. Author AGAS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To study the host-guest interactions of α-, β- and γ-cyclodextrin with herbicide bifenox.
Study Design: Binding constants of the complexes were determined by Benesi-Hildebrand method and stoichiometry of the complexes was confirmed by Job's method. In addition, by means of FT-IR and ^{1}H-NMR spectral analysis, the host-guest interaction of inclusion complexes was deduced.
Place and Duration of Study: Research Department of Chemistry, Aditanar College of Arts and Science, Tiruchendur, Tamil Nadu, India. July 2013-November 2013.
Methodology: Absorption spectrum was recorded with a Systronics-2201 UV-visible spectrometry. FT-IR spectra were obtained with Shimadzu FT-IR spectrometer using KBr pellet. ^{1}H-NMR spectra were recorded with Bruker 300 MHz spectrometer.
Results: The observed results of this study indicate the favoured modes of inclusion of bifenox inside the cavity of cyclodextrins. The experimental results show that the mode of inclusion is the

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benzene ring with-C-Cl part of the bifenox molecule into the cyclodextrin cavity.
Conclusion: UV-visible, FT-IR and ^{1}H-NMR studies proved the formation of inclusion complex between cyclodextrins and bifenox in solution and solid state.

Keywords: Bifenox; cyclodextrin; herbicide; inclusion complex; binding constant.

1. INTRODUCTION

Agrochemicals which are applied to control or kill undesired plants are known as herbicides. By means of their application they are widespread, persist into the soil and thus they represent potential risk to human genetic material. Bifenox (BX, methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate) is a diphenyl ether herbicide provides effective control for broad-leaf weeds and grasses in many crops such as cereal, maize, sorghum, soyabeans and rice. BX has low water solubility of about 0.35 mg per lit. at 20ºC. It acts by cellular membrane disruption of plants and inhibit photosynthesis. BX and their degradation products have toxic, carcinogenic, mutagenic and teratogenic potentials and show varying degrees of persistence in the environment. They affect on the endocrine systems of non-target organisms [1]. To minimize the toxicity of these compounds in the environment, new controlled release systems are emerging that also aim to increase the effectiveness of herbicides while minimizing their environmental impacts and aiding sustainable development. One such method is to make inclusion complex with host molecules.

Cyclodextrins (CDs) have emerged as a new material to improve herbicide's photostabilization and solubility [2-4]. CDs derived from natural starch seem promising as they are biodegradable and environment friendly [5]. CDs are characterized by a truncated cone structure with hydrophobic interior and hydrophilic exterior [6]. The cavity allows size, shape and polarity-based synthetic pesticides with the formation of inclusion complexes [7]. The stability of the complex is related to the amount of water released from CD upon the formation of inclusion complexes with the guest molecule. There is much interest in manipulating the complex forming ability of CDs with a view to developing applications.

A recent approach to reduce herbicides level in the environment involves the development of controlled release formulations since less active ingredient needs to be applied for maintaining the herbicidal efficacy [8]. The application of CDs as solubility-enhancing agents for the formation of poorly water soluble, volatile herbicides have been investigated [9]. Pushpa R Gopalan et al. [10] prepared and characterized β-CD and hydroxypropyl-β-CD complexes of the herbicide isoproturon. Saikosin et al. [11] prepared inclusion complexes with the insecticide carbaryl to obtain formulations with lower toxicological effects. They observed a solubility increase of 18.4-fold when the insecticide was complexed with methyl-β-CD, but showed a lower toxicity than commercial carbaryl. Complexation of 2,4-dichlorophenoxyacetic acid (2,4-D) with CD noticed some changes in the properties of 2,4-D, and the removal of this herbicide previously adsorbed on the soil has been improved using β-CD solution [12,13].

In the present work an attempt has been made to use α-,β- and γ-CDs as host molecules to encapsulate BX. The complexes were prepared and were characterized by UV-visible, FT-IR and ^{1}H NMR spectroscopy. Also this study attempts to identify the most appropriate complexation agent among the three CDs. It is our special interest to explore the binding ability of CDs which will provide a useful approach to achieve CD based agro products with high water solubility, high bioavailability and low toxicity.

2. MATERIALS AND METHODS

2.1 Chemicals

BX, α-CD and γ-CD were supplied by Sigma-Aldrich, β-CD was purchased from Hi-media and all these were used as such without further purification. All other materials were of analytical reagent grade. Double distilled water was used throughout the study.

2.2 Binding Constant Study

Stock solutions of BX (1×10^{-3} M) and appropriate CDs (1×10^{-3} M) were prepared by weighing a known amount and dissolved them in ethanol and water respectively. A known volume of the BX was mixed with different concentrations of CD ($0\text{-}9 \times 10^{-3}$ M) and diluted to 10 mL. These solutions were stirred for 24 h. UV spectra of the

inclusion complexes, pure CDs and BX were recorded by using systronics 2201 UV-vis spectroscopy.

2.3 Job's Continuation Variation Study

The solutions of BX and CDs were prepared in 1 × 10^{-3} M concentration and they were mixed at different volumes in such a way that the total concentration of BX and CD should be constant ([BX] + [CD] = constant). The absorbance of each solution was determined by UV-vis spectroscopy. The stoichiometry of the complex was then determined from the plot of ΔOD *vs.* mole fraction of BX.

2.4 Preparation of Inclusion Complexes of CD with BX

BX-CD ratio 1:1 complexes were prepared by mixing an equimolar amount of the BX and the appropriate CD. The solution after mixing was stirred for 48 h, filtered and washed with small amount of ether to remove any uncomplexed substance. These complexes were dried in an air oven at 60ºC for 4 h.

3. RESULTS AND DISCUSSION

3.1 UV-visible Spectroscopic Analysis

The formation of inclusion complex in aqueous solution between BX and α-, β- and γ-CDs as host can be detected by spectrophotometric methods. Complete spectrophotometric scans between 200 and 400 nm were performed to monitor any changes in the UV spectra of the BX by the addition of CDs. BX (Fig. 1) has absorbance maxima at 254 nm.

Modification of UV spectra of BX in the presence of CDs provides evidence for the formation of an inclusion complex (Fig. 2). CDs have no absorption in the range 200-400 nm. As CD concentration increases the absorbance of guest also increases in the absorption spectrum. This suggests that chromophore of the guest is transferred from an aqueous medium to non-polar CD cavity. This may be accompanied with perturbation of electronic energy levels of BX by direct interaction with CDs, by exclusion of solvating water molecules or by combination of these two effects. Although, only small shifts are observed on UV spectra of included guests the method is often used to detect inclusion complexation [14,15]. As CD concentarion is increased, a small red shift is seen in the case of all the three CDs. The shift towards higher wavelength in the spectra of the complexes may be attributed to the formation of hydrophobic interactions.

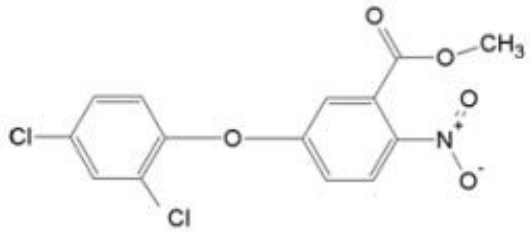


Fig. 1. Structure of bifenox

These spectral observations noted after the addition of α-, β- and γ-CDs to BX indicate the occurrence of an inclusion process, where the BX molecule bind to the CD cavity.

Binding constants (K_b) between BX and CDs in the inclusion complex can be determined by UV method using the absorption changes of BX in the presence of different CD concentration. From the absorption changes, binding constants can be calculated using the Benesi-Hildebrand (B.H) equation [16]. The binding constant value for the inclusion complexes was calculated from the slope and intercept values by applying least-squares fit to the plots of ([host].[guest])/ΔOD vs. ([host] + [guest]).

$$\frac{[CD][substrate]}{\Delta OD} = \frac{[CD]+[substrate]}{\Delta\varepsilon} + \frac{1}{k_b \Delta\varepsilon} \quad (1)$$

Where, ΔOD is the difference between the absorbances of free and complexed guest, [guest] and [host] are the equilibrium concentrations of BX and CD, respectively. $\Delta\varepsilon$ is the difference between the extinction coefficients of free and complexed guest. Fig. 3 shows the plots of ([host]. [guest]/ΔOD *vs.* ([host] + [guest]). The concentration of BX was kept at 1×10^{-3}M, while the concentration of hosts was changed from 1 × 10^{-4} M to 9 × 10^{-4} M.

The calculated K_b value for the inclusion complexes are summarized in Table 1. For all the three inclusion complexes, the dependencies were linear in the investigated concentration range, confirming that the stoichiometry of the inclusion complexes in solution is 1:1.

A comparative study of the K_b values shows that the highest value is observed when β-CDs used. The obtained K_b values show that β-CD exhibits more affinity towards BX than α- and γ-CDs. The greater stability constant of β-CD-BX than α-CD-BX would be related to the larger cavity size of β-CD, which can accommodate guest molecule more comfortably. The K_b value of γ-CD-BX complex is lower compared to β-CD-BX complex. This result reflects the effect of the size of the CD cavity on the formation of inclusion complex. The large internal cavity diameter of γ-CD would result in an easy path for the BX molecule to escape from γ-CD cavity. In this case the main driving force for inclusion complex formation seems to be the hydrophobic/hydrophilic interactions. The present study shows that β-CD offers more stable environment for complex formation with BX molecule. It is interesting to note that both α- and γ-CDs behave alike in stabilizing, in spite of the larger cavity size of the latter. This may be attributed to the higher solubility of these two CDs in water while β-CD being the less soluble one provides a better and tighter fit for the guest.

Table 1. Binding constant (K_b) values of BX with α-, β- and γ-CDs

Complex	Binding constant (M^{-1})
α-CD-BX	301
β-CD-BX	1422
γ-CD-BX	385

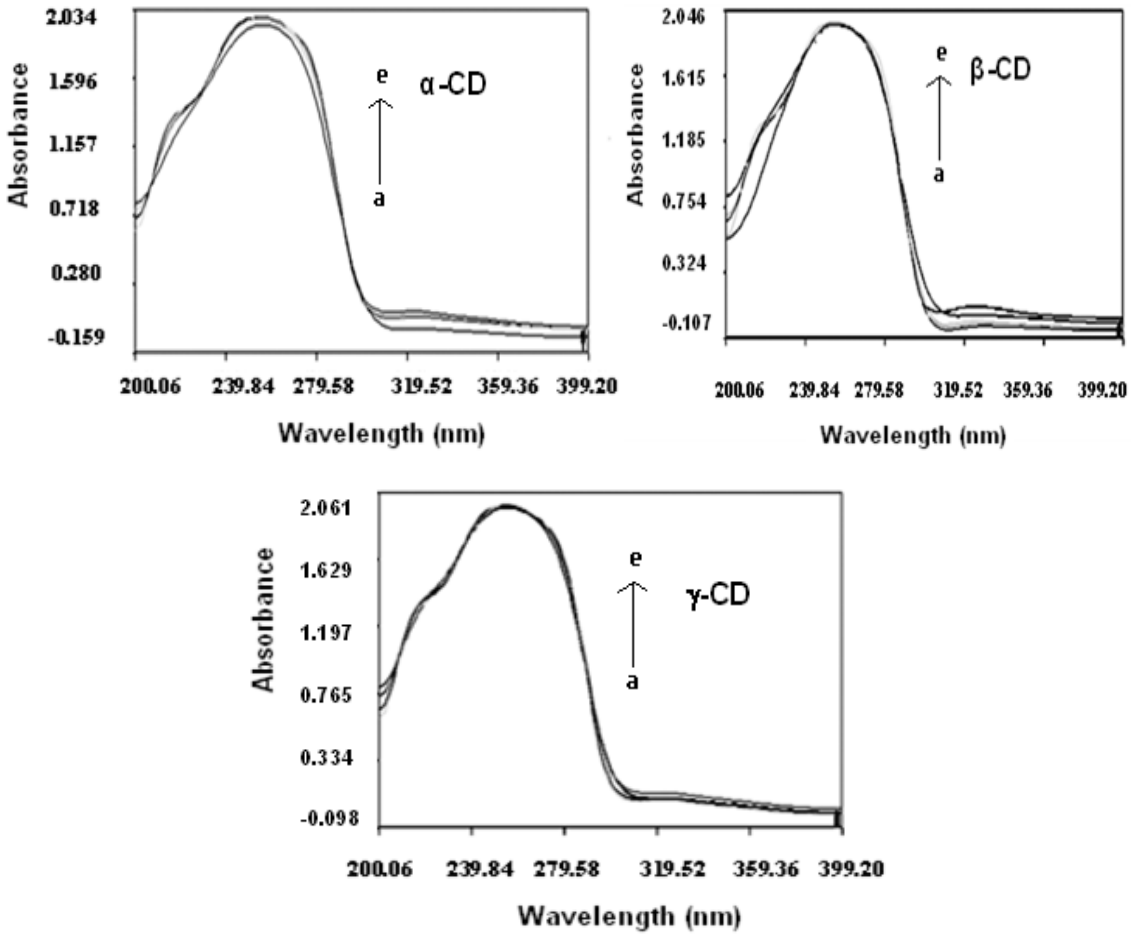


Fig. 2. Absorption spectra of bifenox with different concentrations of CDs; Curves a-e : 0, 3, 5, 7, 9 × 10-4 M of CDs

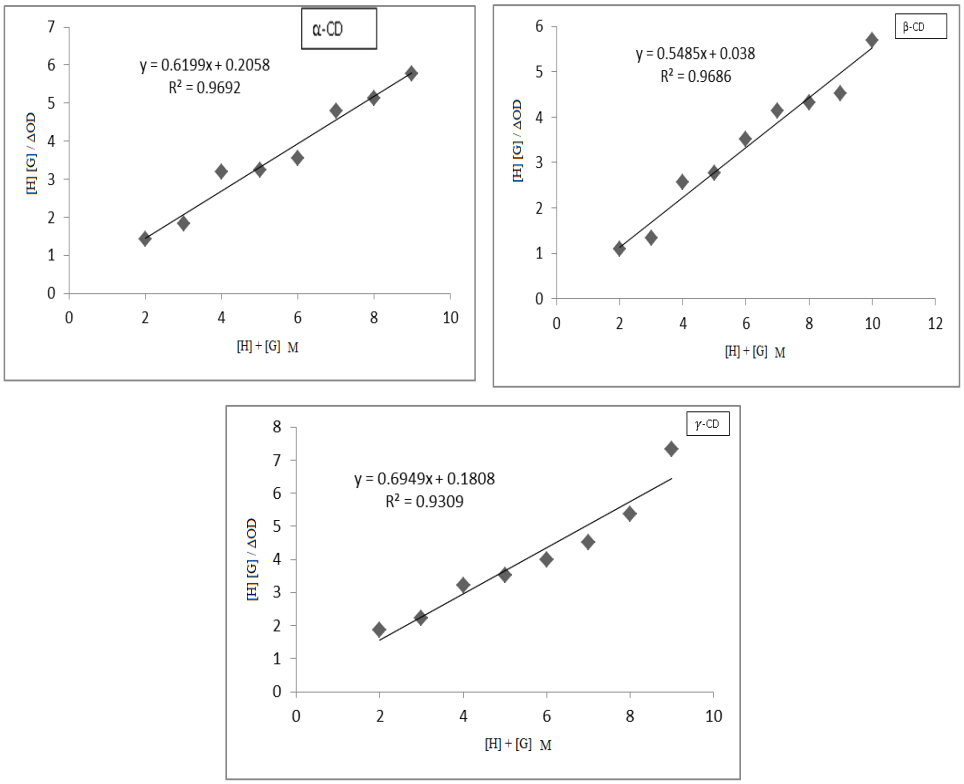


Fig. 3. Benesi- Hildebrand plot for 1:1 complex of BX with CDs

3.2 Job's Plot

The stoichiometry of BX:CD inclusion complex is further confirmed by using Job's continuous variation method. According to continuous variation method a physical parameter of a set of samples is directly related to the molar fraction of its components. Fig. 4 shows the change in optical density (ΔOD) against mole fraction of BX. In this plot (OD) is maximum at a mole fraction of 0.5 which indicates the stoichiometry of the complex between BX and α-, β- and γ-CDs is 1:1 [17], which is in agreement with the stoichiometry suggested from the Benesi-Hildebrand study.

3.3 Characterization by FT-IR Spectroscopy

FT-IR analysis was made to verify the inclusion of the herbicide BX into CDs. The FT-IR spectra of pure BX and its complexes with three CDs are shown in Fig. 5. The FT-IR spectrum of pure BX shows its characteristic absorption bands: the band at 1739 cm^{-1} assigned to the carbonyl stretching of BX carboxyl ester, the band at 1340 cm^{-1} to the methyl stretching vibration, the band at 1253 cm^{-1} to the ether asymmetrical stretching, the band at 648 cm^{-1} to the aromatic phenyl ring vibration, the band at 1060 cm^{-1} to the aromatic C-Cl stretching vibration, the peaks observed at 1597 cm^{-1} due to the characteristic stretching of aromatic nitro group and the peaks observed in the region 827-916 cm^{-1} assigned to phenyl ring. Table 2 presents the FT-IR frequencies of BX in pure state and in the complex state.

The characteristic peak of the ester carbonyl stretching band (1739 cm^{-1}) of BX is unchanged during complexation indicating that solid BX and CDs do not have direct interactions. The characteristic stretching vibration of -C-Cl band is shifted to lower frequency in all inclusion complexes. Further, the intensity of the bands is reduced. These results clearly show that the benzene ring having -C-Cl end of BX is encapsulated into CD cavity. The intensity of characteristic stretching vibration of –C-O-C- (1253 cm^{-1}) is also reduced compared to free BX indicates the mode of inclusion of BX into CD cavity via the -C-Cl end of benzene ring. The insignificant change in the characteristic

stretching vibrations of aromatic nitro group and carbonyl group indicates that the nitro and ester groups are projected above the CD rim. The shift of the band corresponding to the methyl stretching vibration in complexes from 1340 to 1342 cm^{-1} suggests the electronic change around the methyl group, likely due to the formation of new hydrogen bonding between the carbonyl of BX and the OH of CDs.

The O-H stretching frequency appears at 3467 cm^{-1} in CD has decreased due to complexation. The absorption bands of the valence vibrations of the C-O bonds in the ether and hydroxyl groups of CD in the region 1200 -1030 cm^{-1} are slightly broadened in the inclusion complexes. In the inclusion complex, the characteristic absorption maxima observed at 847, 759 and 707 cm^{-1} are assigned to glucopyranose unit for all CDs. The FT-IR frequencies of CD with solid inclusion complexes are listed in Table 3. A very good correspondence between our data referring to the IR spectra of CDs and the literature ones has been obtained [18-20].

Table 2. FT-IR frequencies of BX in pure state and in the complexes

Type of stretching vibration	Wave number (cm^{-1})			
	BX	α-CD-BX (1:1)	β-CD-BX (1:1)	γ-CD-BX (1:1)
C=O	1739	1739	1741	1739
methyl	1340	1342	1340	1344
-C-O-C-	1253	1253	1253	1253
-C=C-	648	650	651	651
C-Cl	1060	1031	1028	1029
C-H	827	829	831	835

[a]*Pellet technique using KBr*

Table 3. FT-IR frequencies of CDs and its BX complexes

Type of vibration	Free CD	Wave number (cm^{-1})		
		α-CD-BX	β-CD-BX	γ-CD-BX
O-H stretching	3467	3465	3456	3460
C-Hstretching	2926	2926	2920	2924
C-H bending	1420	1415	1410	1412
O-H bending	1337	1331	1328	1329
C-O bending in primary and secondary alcohol	1166, 1094	1165, 1090	1155,1084	1162,1087
Skeletal vibrations involving α-1,4 linkages	942	937	932	935

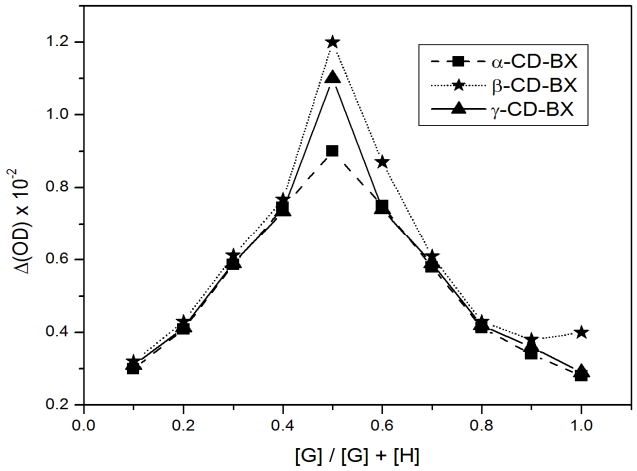


Fig. 4. Job's plots for the complexes of bifenox with CDs

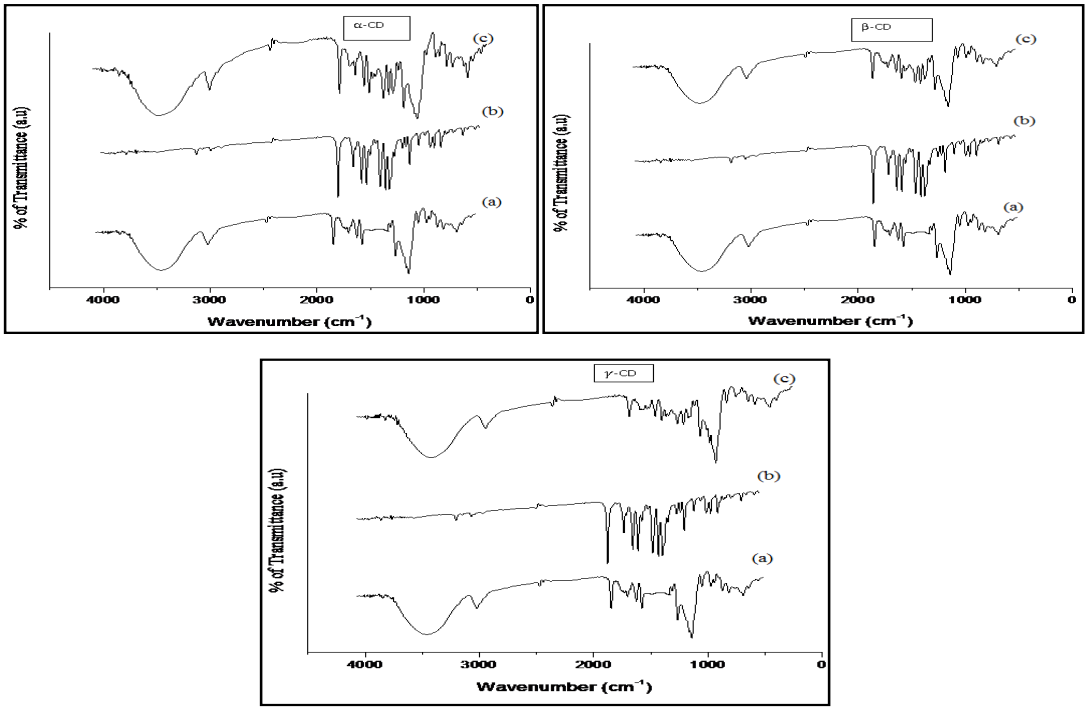


Fig. 5. FT-IR spectra of 1:1 complex of bifenox with α-, β- and γ-CDs: (a) CD; (b) bifenox; (c) complex

These significant change in frequencies of the complexes when compared with those of the CDs and BX, indicate partial or complete shielding of chromophores in the CD cavity and are therefore rationalized as being indicative of complex formation. Further FT-IR studies clearly indicated that the dichlorophenoxy group ring is positioned inside the CD cavity, with the methyl ester exposed outward, away from the CD cavity.

3.4 Proton NMR Spectra

Nuclear Magnetic Resonance spectroscopy (NMR) is one of the most useful techniques to study interactions of CDs with guest compounds. It is relatively easy to apply and it is the only technique that provides information on the right orientation of the guest molecule inside the cavity. Host-guest molecular interactions are manifested by changes in the chemical shifts of the protons involved in complex formation [21]. Large effects are usually observed for that part of the guest molecule, which is immersed in the CD cavity.

The ^{1}H NMR spectroscopy studies of BX with α-, β- and γ-CDs were carried out to gain insights into the complexation mode of BX. The values of chemical shifts, δ, for different protons in CD with solid inclusion complex and BX with solid inclusion complex are listed in Tables 4 and 5. It is observed that the chemical shifts due to the proton shielding are smaller than 0.1 ppm (Fig. 6).

The observed order of difference in δ values is Δδ β-CD:BX > Δδ γ-CD:BX > Δδ α-CD:BX. This indicates the complexation between β-CD and BX is stronger than in α- and γ-CD. Correlation of the H-3 and H-5 protons of the CD to the protons of the guest is strong evidence for the formation of an inclusion complex. In the presence of α-CD, all protons of BX are shielded to some degree, the exception being the proton adjacent to the nitro group (H-a), which are not shielded. Strong spatial correlations were observed between H-b, H-c and H-d of BX protons and the H-3 / H-5 protons of α-CD indicating deep inclusion of the chlorine-substituted ring into the CD cavity [22,23]. Similar spatial correlations were observed between BX and β-CD, indicating a similar mode of inclusion. The disparity in Δδ values of the aromatic protons may be attributable to complexation-induced changes in the

shielding/de-shielding effects (i.e. inductive and mesomeric effects) of the substituent groups. Additional proton interactions between the H-3 proton of β-CD with those of BX is more up-fielded indicate that the BX is included more deeply in the β-CD cavity than for α-CD. There appears to be a different mode of binding of BX to γ-CD, strong shielding correlation exists only with H-3 signal and not with H-5 signal. In contrast to α- and β-CD complexes, γ-CD complex has less difference in Δδ for H-5 than H-3. Partial inclusion of the guest inside the cavity occurs when Δδ H-3 > Δδ H-5 and total inclusion takes place if Δδ H-3 < Δδ H-5.Considering the values of Δδ for H-3 and H-5 it is concluded that the inclusion of BX is less in α- and γ-CD and more in β-CD. The less difference in chemical shift is supposed to be due to the relatively high polarity and solubility of the guest in aqueous media [24]. The change in chemical shift of H-g proton indicates the existence of hydrogen bond between C=O group of ester and –OH of CD molecule. The observed up-field shift changes in the inner CD cavity protons and downfield shifts in the BX can be explained in terms of ring current effect of BX aromatic ring that enter the host cavity and thus confirms the formation of BX-CD complex [25].

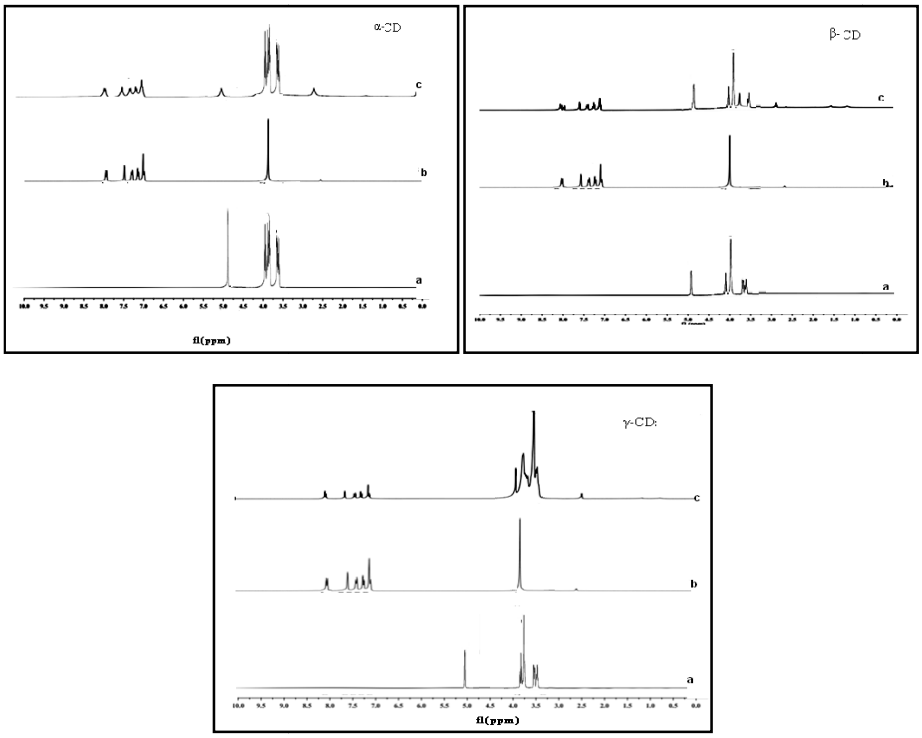


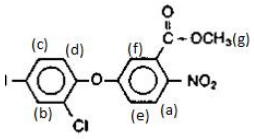
Fig. 6. 1H NMR spectra of 1:1 complexes of bifenox with α-, β- and γ-CDs (a)CD, (b)-bifenox and (c)-complex

Table 4. [1]H NMR chemical shift (δ) values of CDs and their complexes with BX[a]

Proton	δ		Δ δ	δ		Δδ	δ		Δδ
	α-CD	BX-α-CD		β-CD	BX-β-CD		γ-CD	BX-γ-CD	
1	4.96	4.95	-0.01	4.99	4.98	-0.01	5.01	5.01	0.00
2	3.53	3.54	0.01	3.57	3.56	-0.01	3.56	3.55	-0.01
3	3.91	3.86	-0.05	3.88	3.79	-0.09	3.86	3.80	-0.06
4	3.49	3.48	-0.01	3.53	3.50	-0.03	3.49	3.49	0.00
5	3.76	3.71	-0.05	3.77	3.65	-0.12	3.80	3.77	-0.03
6	3.80	3.81	0.01	3.80	3.82	0.02	3.87	3.89	0.02

[a]*DMSO-$d_6$solvent*

Table 5. ^{1}H NMR chemical shift values of BX and its complexes with CDs[a]

Bifenox	Proton	Chemical shift δ (ppm)						
		BX	BX: α-CD	Δδ	BX: β-CD	Δδ	BX: γ-CD	Δδ
	H-a	8.11	8.12	0.01	8.12	0.01	8.13	0.02
	H-b	7.68	7.75	0.07	7.78	0.10	7.75	0.07
	H-c	7.47	7.53	0.06	7.54	0.07	7.55	0.08
	H-d	7.44	7.50	0.06	7.52	0.08	7.50	0.06
	H-e	7.31	7.34	0.03	7.32	0.01	7.34	0.03
	H-f	7.14	7.19	0.05	7.17	0.03	7.18	0.04
	H-g	3.88	3.89	0.01	3.91	0.03	3.92	0.04

[a]*DMSO-$d_6$solvent; ($\Delta\delta = \delta_{complex} - \delta_{free}$)*

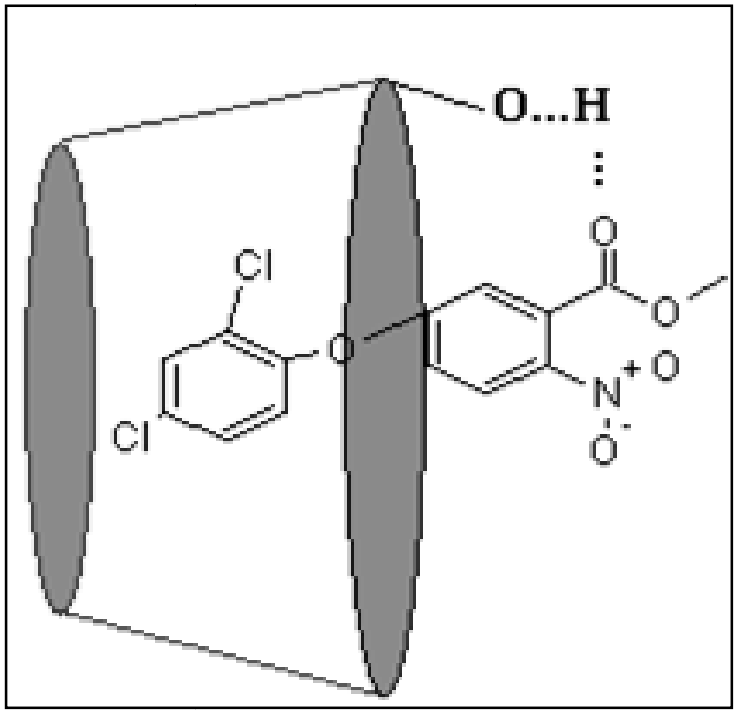


Fig. 7. A plausible structure proposed for bifenox-cyclodextrin

4. CONCLUSION

An environmentally friendly compound derived from natural starch, CDs appear promising to be used as a future formation additive for commercial BX. CDs are hydrophilic in nature but also contains a hydrophobic cavity within its molecular structure. Fig. 7 above explains the possible structure proposed for inclusion complexes between CD and BX. The occurrence of BX within the cavity of CDs was verifies by the techniques including UV, FT-IR and NMR. Due to the resistance of the complexed BX to hydrolysis that would otherwise convert to dichlorophenol, the complexed CD could be used as better herbicide. The BX–CD complex also dissolves quickly in water and thus available immediately to target grasses. The complexation reduces the sorption of BX by soil and may concurrently mobilized additional adsorbed herbicides and other organic pollutants for enhanced biodegradation.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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