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Complexation of Triclopyr Butoxy Ethyl Ester with β-Cyclodextrin

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β-cyclodextrin (β-CD), a macro-cyclic oligosaccharide exhibits the property of forming inclusion complexes with various molecules. These complexes display some improved properties of starting molecule such as, increase of aqueous solubility, improvement in stability as well as reduction of bad odor and/or toxicity of molecules. The formulation of an inclusion complex of β-CD as the host molecule and triclopyr butoxy ethyl ester, a selective systemic herbicide, as guest molecule has been studied as an initial step towards the improvement in the conventional herbicide formulations. The interaction of triclopyr butoxy ethyl ester with β-CD produced the formation of an inclusion complex. Three processing methods (kneading, co-precipitation and co-evaporation) were used to prepare solid inclusion complexes. X-ray diffraction (XRD), differential scanning calorimetry (DSC) and ultra-violet (UV) spectroscopy techniques were used to study the complexation of this herbicide. The objective of the present work was to study the complexation and enhanced aqueous solubility of triclopyr butoxy ethyl ester. Phase solubility study suggested the existence of a 1:1 complex between herbicide and β-CD. XRD and DSC analysis indicated the existence of an inclusion complex of herbicide with β-CD. Dissolution rate study was conducted so as to study dissolution properties of complexes. The dissolution rate of the complexed herbicide in aqueous media was considerably improved as compared with the uncomplexed herbicide. The study also attempts to compare the various methods of complex formation. The best results were obtained when inclusion complexes were prepared by co-precipitation method. Findings of this paper will allow more rational applications of herbicide with increase in its efficiency.

Keywords β-cyclodextrin, inclusion complex, triclopyr butoxy ethyl ester, solubility

Introduction

Cyclodextrins (CD's) are macro-cyclic oligosaccharides, containing 6(α-CD), 7(β-CD) or 8(γ-CD) D-glucose units formed from the enzymatic degradation of starch by bacteria. These are natural, non-toxic compounds harmless to microorganisms and hence, not

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noxious for the environment (1, 2). The most important structural feature of these compounds is their torous-like shape, with a hydrophobic interior cylindrical cavity and hydrophilic faces (3). It is well known that they are capable of forming inclusion compounds both in solution and in solid state with a variety of guest molecules, which are placed in their hydrophobic interior cavity (4). The mechanism of complex formation is well discussed (5).

These inclusion complexes find a variety of applications in pharmaceuticals (6), pesticides (7), etc. In the field of agrochemicals, these inclusion complexes are finding many important applications. The improvement in physicochemical properties such as enhancement of solubility, shown by some publications (8–12), increase in stability against oxidation, heat degradation of unstable pesticides, (13–15) reduction of unpleasant taste, odor and controlled release (16) has attracted the attention of many formulation experts towards β-CD. Some publications confirm the prediction that, in the next years, a rapid development can be expected in the applications of CDs.

The present work describes the interaction of triclopyr butoxy ethyl ester with β-CD. Triclopyr butoxy ethyl ester is a selective systemic herbicide, which is used to control unwanted woody and herbaceous weeds in pasture and woodlands. It is a herbicide that mimics auxin, a plant growth hormone, thus disrupting the normal growth and viability of wild plants (17). It inhibits growth of mycorrhizal fungi, a beneficial fungi that increases wild plant ability to take up nutrients (18). This herbicide is very mobile in soil because molecules of herbicide are not strongly held by soil (19). In soil, triclopyr butoxy ethyl ester has a half-life ranging from 1.1 to 90 days depending on soil type. Several resources have reported a 46-day half-life for this herbicide (20). It also has low volatility on soil surface.

Triclopyr butoxy ethyl ester was first registered as an herbicide in the U.S. in 1979 (21). It is an amber-colored oily liquid having a kerosene-like odor. It has poor water solubility, 23 mg/liter and a vapor pressure of 1.5×10^{-6} mmHg at 25°C (17).

The rationale for the selection of this herbicide is mainly the action of the pesticide, and its poor solubility in water. Some publications have discussed the importance of solubility of systemic herbicides in their efficacy (22). In light of these findings, it was thought that the limitations in the efficacy of the herbicide, because of its poor solubility, could be overcome by its complex formation with β-CD (8, 11, 12).

The principal objective of the present work is to investigate complexation, as well as the possibility of improving the aqueous solubility and dissolution properties of triclopyr butoxy ethyl ester via inclusion complexation with β-CD. The formation of such inclusion complexes is confirmed by a variety of methods and techniques, such as phase solubility determination, X-ray diffraction (XRD) and differential scanning calorimetry (DSC). To evaluate the enhancement in the dissolution rate of triclopyr butoxy ethyl ester-β-CD complexes, dissolution tests were performed using the USP 23 paddle method.

Experimental

Materials and Methods

Triclopyr butoxy ethyl ester was considerately supplied by Gharda Chemicals Ltd. (Maharashtra, India) and β-cyclodextrin (β-CD) (99%) by Signet Chemicals Ltd. (Mumbai, India). All other chemicals were of analytical grade.

Preparation of Samples

The triclopyr butoxy ethyl ester-β-CD inclusion complexes were prepared by co-precipitation, co-evaporation and kneading methods (8). A physical mixture of β-CD and triclopyr butoxy ethyl ester was also prepared by simple mechanical mixing. It was used as reference in characterization. All the complexes were prepared with 1:1, 1:2, and 1:3 ratios (Figure 1).

Kneading Method

In the kneading method, triclopyr butoxy ethyl ester and β-CD were mixed in 1:1, 1:2 and 1:3 molar proportions in mortar for 10 min. During this process, 5 ml methanol was added to the mixture to maintain a suitable consistency. These pastes were further kneaded for 45 min. The obtained mass was dried in vacuum desiccators at room temperature for 72 h. The dried complex was gently grinded to a fine powder and characterized.

Co-evaporation Method

In this method, triclopyr butoxy ethyl ester and β-CD, the ratio above were dissolved in 300 ml of methanol at 50°C. The solution was stirred for 30 min. The solvent was removed using a rotary evaporator at 40°C. The complexes obtained as powders were further dried in vacuum desiccators at room temperature for 72 h.

Co-precipitation Method

β-CD was dissolved in 150 ml distilled water at 55°C and triclopyr butoxy ethyl ester was dissolved in 30 ml of methanol and heated at 60°C. Both solutions were mixed and stirred at 70°C for 1 h. In addition, the solution was cooled to room temperature and stirred at room temperature for 24 h. The precipitate obtained was filtered and washed with 5 ml of methanol to remove any uncomplexed herbicide. The washed precipitate was dried in vacuum desiccators for 72 h at room temperature. The dried precipitate was grinded to a fine powder.

Characterization of β-CD Complexes

Phase-Solubility Study. To investigate stoichiometry of the complexes, the phase solubility study was performed (23). Solutions containing various concentrations of β-CD were added to a definite amount of triclopyr butoxy ethyl ester. The flasks were sealed and shaken at ambient temperature for 48 h. After equilibrium, the samples were filtered with a syringe through Wattman Filter paper no. 40 and analyzed spectrophotometrically at 231 nm. using a Jasco V-530UV-visible spectrophotometer.

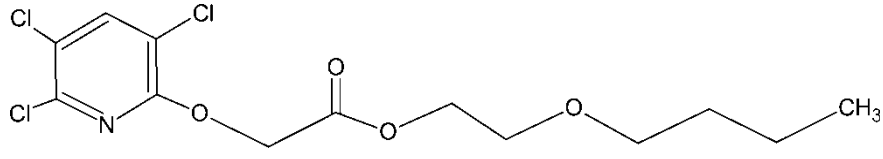

Figure 1. Structure of triclopyr butoxy ethyl ester.

X-Ray Diffraction (XRD)

X-Ray diffractograms of β-CD, triclopyr butoxy ethyl ester and different complexes were obtained on a PANalytical X'Pert PRO diffractometer. The conditions used were as follows: 2θ Ni-filtered Cu K α radiation, detector-Xcelerator, scanning speed-0.0016°/sec.

Differential Scanning Calorimetry (DSC)

DSC was carried out on a Perkin-Elmer DSC 7 apparatus. Samples of about 10 mg. were put into aluminium pans and covered with lids, which were pierced to permit the gas release during the heat process, which was performed under nitrogen gas atmosphere. The conditions were as follows: Heating rate: 10.0 C/min. Temperature range from 80 to 180°C.

Dissolution Rate Study

The dissolution rate studies of solid complexes were performed according to the USP 23 paddle method (24). The dissolution medium was distilled water (1000 ml). The stirring speed was 50 rpm, and the temperature maintained at 37°C. Aliquots (5 ml) were withdrawn at various time intervals (5, 10, 15, 30, 60, 90 and 120 min) and analyzed spectrophotometrically at 231 nm.

Results and Discussion

Phase Solubility Study

The phase solubility diagram is presented in Figure 2. The phase solubility diagram was obtained by plotting an amount of triclopyr butoxy ethyl ester dissolved (mM) vs. the amount of β-CD added (mM). This shows that the aqueous solubility of the herbicide increases as a function of β-CD concentration. It is observed tha, the phase solubility

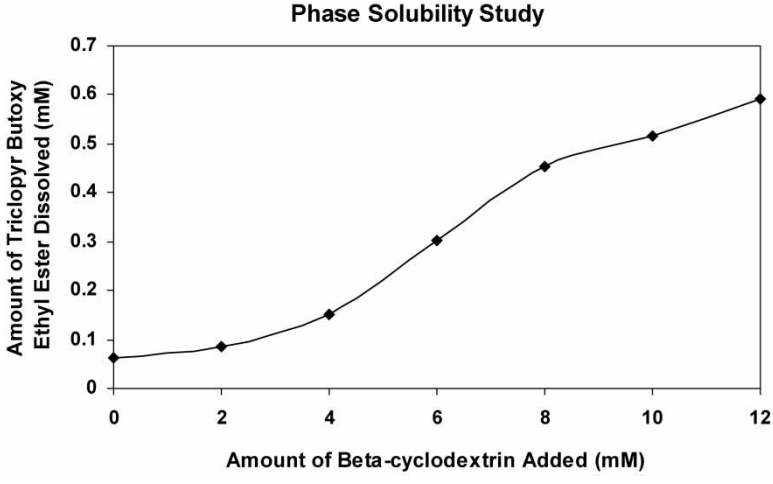

Figure 2. Phase solubility diagram of triclopyr butoxy ethyl ester- β-CD system in water.

diagram of triclopyr butoxy ethyl ester in the presence of β-CD (Figure 2) can be classified as the type *B*s. It can be concluded from the *B*s type of curve obtained that there is a formation of an insoluble complex in the solution at high concentration of β-CD. The stoichiometry of the complex can be derived from the initial ascending part of this curve, which is a straight line with slope 0.0064, which indicated that at least one complex with 1:1 ratio was formed in the solution. The apparent stability constant $K_{1:1}$ was calculated from Equation (1). In our case, the stability constant $K_{1:1}$ was observed to be $1610.30\,M^{-1}$.

$$K_{1:1} = \text{slope}/\ S_0\ (1 - \text{slope}) \tag{1}$$

where, S_0 is the intercept.

X-Ray Diffraction (XRD)

X-ray diffraction (XRD) studies have been carried out. The XRD pattern of the complexes should be different from those corresponding to β-CD (11). XRD patterns of pure β-CD (Figure 3a), triclopyr butoxy ethyl ester (Figure 3b) and their complexes (Figures 3c–3f) obtained under different processing methods are included. XRD pattern of complexes was different from those corresponding to crystalline β-CD. The XRD pattern of β-CD and triclopyr butoxy ethyl ester shows good crystallinity. Due to the physical interaction between β-CD and herbicide, complexes of physical mixture (Figure 3c) and kneading sample (Figure 3d) show overlapping effect corresponding to pure β-CD diffractogram. The XRD pattern of physical mixture and kneaded complex is somewhat similar in nature. In contrast, complexes obtained by co-precipitation (Figure 3e) and co-evaporation method (Figure 3f), exhibit a large decrease of the diffraction peaks corresponding to β-CD and triclopyr butoxy ethyl ester diffractograms; suggesting that the complexes are less crystalline or amorphous. These results could confirm the formation of inclusion complexes.

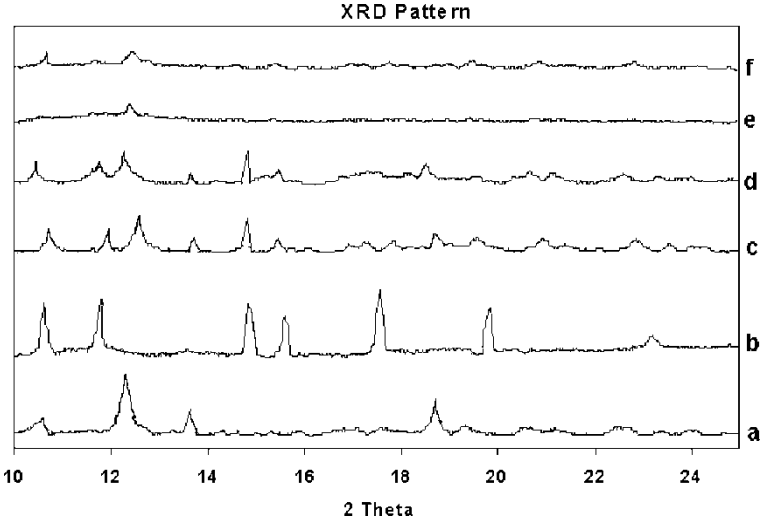

Figure 3. X-ray diffractograms of (a) β-CD, (b) Triclopyr butoxy ethyl ester and 1:1 triclopyr butoxy ethyl ester-β-CD systems of, (c) physical mixture sample, (d) kneaded sample, (e) co-precipitated sample and (f) co-evaporated sample.

Differential Scanning Calorimetry

The DSC curve of β-CD (Figure 4a) shows an increasing broad endothermic peak (137°C) in the range of 95–153°C which corresponds to the dehydration process i.e., removal of water molecules. DSC thermogram of triclopyr butoxy ethyl ester (Figure 4b) exhibits one small sharp endothermic peak centered at 131°C. The absence of interaction between β-CD and herbicide via the physical mixing (Figure 4c) process is clearly visible due to the presence of two peaks at 133°C and 139°C, which correspond to the triclopyr butoxy ethyl ester and β-CD, respectively.

Similar observation is visible, when kneading method (Figure 4d) was used to obtain the complex. Also, in Figure 4C and 4d, the dehydration effect of β-CD, is slightly decreased which is indication of lower water content in the internal cavity of β-CD molecule.

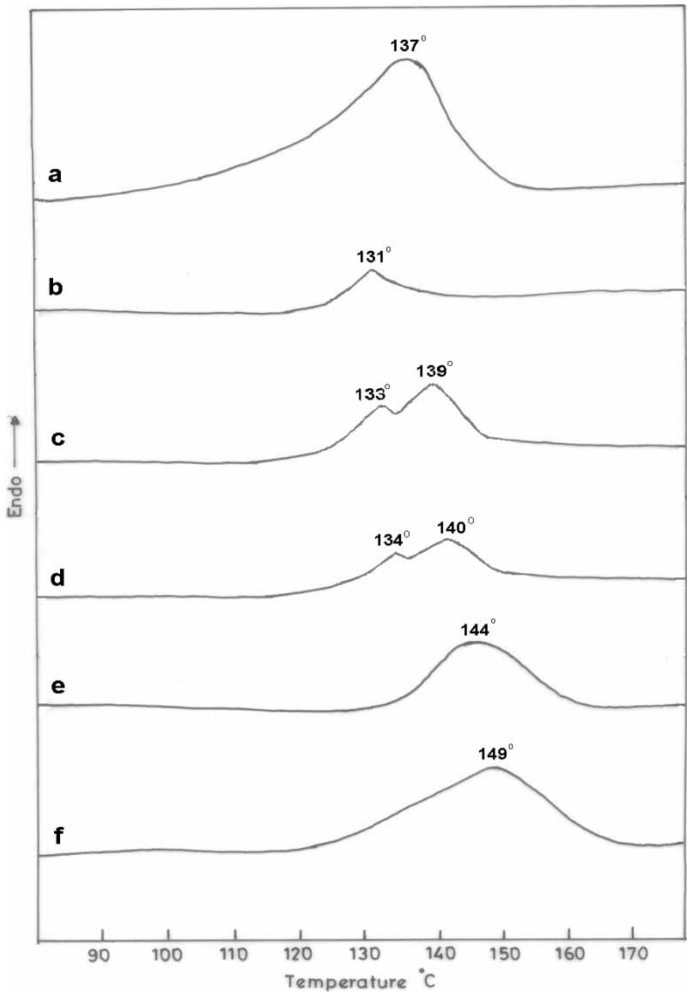

Figure 4. DSC thermograms of (a) β-CD, b) Triclopyr butoxy ethyl ester and 1:1 triclopyr butoxy ethyl ester -β-CD systems of, (c) physical mixture sample, (d) kneading sample, (e) co-evaporated sample and (f) co-precipitated sample.

The decrease in the β-CD dehydration endothermic peak at 139°C during the physical mixing method and 140°C during the kneading method may also be due to the complexation of a very small percentage of herbicide within the β-CD cavity with formation of new crystalline structure. However, this complexation takes place to only a small extent and thus is not indicative of complete complexation.

The thermogram of sample obtained via the co-evaporation method (Figure 4e) shows only a single broad endothermic peak centered at 144°C. The complete disappearance of the peaks corresponding to β-CD and herbicide, and appearance of a new broad endothermic peak at 144°C confirms complexation between β-CD and triclopyr butoxy ethyl ester component via inclusion.

Similarly, a result was observed for complex obtained via co-precipitation method (Figure 4f), which also exhibits complete disappearance of β-CD and herbicide peaks and appearance of a new broad endothermic peak centered at 149°C. This confirms complexation between β-CD and triclopyr butoxy ethyl ester component via co-precipitation method.

Furthermore, two new broad endothermic peaks of co-evaporated complex at 144°C and of co-precipitated complex at 149°C appeared to shift at higher temperatures, which indicates an excellent complexation between β-CD and triclopyr butoxy ethyl ester. Among all these methods, co-precipitation method shows good complexation. (Analysis of all samples were carried out on a Perkin-Elmer DSC 7 apparatus and on this type make apparatus endothermic curves are always observed at upward direction).

Dissolution Rate Study

Dissolution profiles of the different complexes having 1:1 ratio are shown in (Figure 5). The dissolution rate of triclopyr butoxy ethyl ester from co-precipitated complex was observed to be faster than other complexes. Pure herbicide dissolved only to extend 18% at the end of 2 h. All the other samples displayed better dissolution of herbicide. The percentage of triclopyr butoxy ethyl ester dissolved from the physical mixture, kneaded, co-evaporated and co-precipitated product was 37%, 45%, 51% and 58%, respectively (Table 1). The percentage of this herbicide dissolved by this ratio of complex prepared by co-precipitation method was 58% which showed better dissolution rates of herbicide as compared to the other methods of preparation.

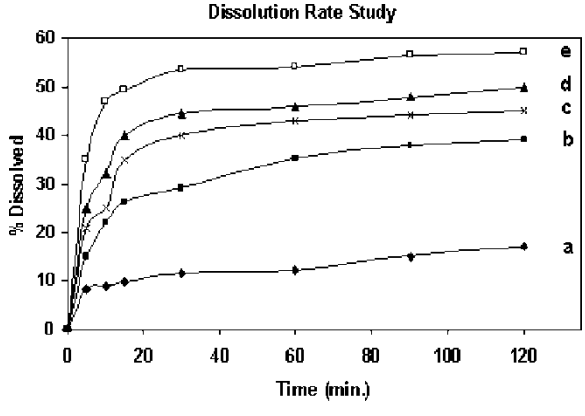

Figure 5. Dissolution profile of triclopyr butoxy ethyl ester -β-CD complex (1:1 ratio) in aqueous media. a) Triclopyr butoxy ethyl ester, b) Physical mixture sample, c) Kneading sample, d) Co-evaporated sample and e) Co-precipitated sample.

Table 1

Dissolution rate study of triclopyr butoxy ethyl ester and triclopyr butoxy ethyl ester-β-CD complexes (1:1 ratio) in aqueous media

	Samples	% Dissolved (after 2 h)
a	Triclopyr butoxy ethyl ester	18
b	Physical mixture sample	37
c	Kneading sample	45
d	Co-evaporated sample	51
e	Co-precipitated sample	58

The dissolution rate profiles of the complexes having 1:2 and 1:3 ratios, the trend was similar to that in the complexes having 1:1 ratio. In all the ratios, co-precipitation complex gave the best results.

However, the molecular geometry within the inclusion complex cannot be accurately deduced from the present results. Although a 1:1 molar complexation may be predicted from the solubility results, and this composition would allow the maximum contact of the herbicide with the apolar cavity of β-CD, additional investigations are also needed. In the same sense, further experimental work is required to understand completely the mechanism of formation of this inclusion complex. They will be the subjects of future study/reports.

Conclusions

The results from this study indicated an interaction between triclopyr butoxy ethyl ester and β-CD. Phase solubility study suggested the existence of 1:1 complex between herbicide and β-CD. The changes in XRD and DSC thermograms of the complexes allowed establishing that triclopyr butoxy ethyl ester forms an inclusion complex with β-CD. The dissolution rate of the complexed herbicide in aqueous media was considerably improved as compared with the uncomplexed herbicide. The increase in the solubility depending on the complexation technique also indicates a complex formation. Among these various complexation methods co-precipitation gave the best results corresponding to inclusion complexation as well as dissolution property of triclopyr butoxy ethyl ester.

The formation of inclusion complex between triclopyr butoxy ethyl ester-β-CD improves some of the physicochemical properties of triclopyr butoxy ethyl ester such as improved solubility in aqueous media so that it can be effectively used in agrochemical formulations such as wettable powders and water dispersible granules. Therefore, the inclusion complexation can be considered to be the initiation step towards obtaining controlled release and/or improved protective formulations of this herbicide.

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