Application of Cyclodextrins in Agrochemistry

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the physical, chemical, and biological properties of guest molecules has been used for the preparation of new formulations of pesticides. CyDs form complexes with a wide variety of agricultural chemicals including herbicides, insecticides, fungicides, repellents, pheromones, and growth regulators [1, 2].

Each CyD has its own ability to form inclusion complexes with specific pesticides, depending on a proper fit of the pesticide molecule into the hydrophobic CyD cavity. The principal advantage is that the binding of pesticide molecules within the host molecule is not fixed or permanent but rather is a dynamic equilibrium. Dissociation of the inclusion complex is a relatively rapid process usually driven by a large increase in the number of water molecules in the surrounding environment [3]. ▌AQ16.3.1▐

Similarly to CyD applications in the pharmaceutical (Chapters 14 and 15) and other industries, the most common benefits of CyD applications in agriculture include, among others, alterations of the solubility of the pesticide, stabilization against the effects of light or biochemical degradation, and a reduction of volatility. In some applications, more than one benefit is obtained by complexation with CyDs. However, the application of these hosts in pesticide formulations is very modest, and represents less than 1% of the CyD literature [4]. Moreover, most of these publications are not directly practice oriented. Instead they deal with the preparation of pesticides@CyD complexes using different oligosaccharides and processing methods and their characterization using a wide variety of techniques.

Among these papers, some are more or less theoretical papers dealing with the correlation between the properties of the new complexes obtained and the properties of the CyDs, pesticides, or external parameters used. Viernstein et al.

[5] compared the abilities of β- and dimethyl-β-CyDs to increase the solubility of the systemic fungicide triflumizole. Pospisil et al. [6, 7] studied the influence of difenzoquat@CyD complexation on the electron-transfer reaction of the herbicide molecule and on its solution conductivity and fluorescence intensity. Ishiwata and Kamiya [8] estimated the depth of guest insertion in CyD inclusion complexes of the organophosphorus pesticides parathion and paraoxon, using rotational strength analysis. Pérez-Martínez et al. [9] employed ^{1}H NMR spectroscopy (see Chapter 9) to confirm the complexation and study structural aspects of the inclusion complexes formed between the herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) and α- and β-CyDs. Also Consonni et al. [10] have used ^{1}H and ^{13}C NMR spectroscopic techniques to establish the three-dimensional structure of the fungicide imazalil@β-CyD complex. A study of the interaction of 18 pesticides with a water-soluble β-CyD polymer (BCDP) demonstrated that the lipophilicity of the majority of them decreased in relation to the strength of the BCDP–pesticide inclusion complex [11].

In addition to the techniques previously mentioned, a wide variety of methods has been used to characterize the new inclusion compounds in solution and in the solid state, in both directly practice-oriented and theoretical papers, to elucidate the relationship between the relative strength of interaction and some surface parameters of the guest molecules. Complexes obtained in solution are frequently studied by phase-solubility, to obtain the stoichiometric ratio for the complex and an apparent stability constant [12–14], but spectral studies including UV, infrared, fluorescence, and NMR spectroscopy (see Section 10.3 and Chapter 9) can also be used for characterization [6, 15–17]. Inclusion compounds obtained in the solid state are frequently characterized using infrared spectroscopy, X-ray diffraction (Chapter 7), scanning electron microscopy techniques [18, 19] (Section 10.6), differential scanning calorimetry (DSC) (Chapter 8) [20, 21], and/or fluorescence (Section 10.3) and voltammetric measurements (Section 10.5) [16, 22].

However, a large number of papers present research in which complexation with CyD is studied using pesticides that really present problems, from both an agricultural and/or an environmental point of view with the aim of obtaining certain benefits, although the majority of these papers do not address the experimental application of the complexes obtained. Most pesticide–CyD complexes have been prepared to improve their solubility in water. Owing to the importance of solubility in foliar translocation and the penetration of systemic herbicides and fungicides, Manolikar and Sawant [13] prepared and characterized β-CyD complexes of the herbicide isoproturon. Saikosin et al. [19] prepared inclusion complexes with the insecticide carbaryl by kneading and freeze-drying processing methods to obtain formulations with lower toxicological effects. They obtained an 18.4-fold solubility increase when the insecticide was complexed to methyl-β-CyD, showing a lower toxicity than commercial carbaryl. Owing to the wide use of the herbicides diuron and isoproturon, considered as important environmental pollutants, Dupuy et al. [23] have prepared and characterized their inclusion complexes with β-CyD in solution and in the solid state.

2,4-D is also one of the most widely used herbicides and causes contamination of

soils and waters owing to its physicochemical properties and persistence. For this reason, some 2,4-D@CyD complexes has been prepared to provide different properties. Although only a slight increase of the herbicide's solubility was obtained after its complexation to β-CyD [12], the removal of herbicide previously adsorbed on the soil was improved by the use of β-CyD solutions [24]. Morillo et al. [25] observed the complete leaching of 2,4-D by the application of β-CyD solution to soil columns in which this herbicide was previously adsorbed. However, preliminary application of CyD to the soil retarded leaching of the herbicide through the soil column, probably because the 2,4-D was adsorbed on the soil though β-CyD adsorbed. ▌AQ16.3.2▌ The complexation of 2,4-D with α-, HP-β-, and PM-β-CyDs has been also studied [18, 20, 26], and 3-, 9- and 17-fold increases of herbicide solubility were found, respectively, relative to the solubility of the uncomplexed compound.

To achieve good biological activity, fungicides must be used dissolved in water, which, in most cases, involves the preparation of ionized derivatives, and, if this is not feasible, the use of organic solvents. For this reason, Lezcano et al. [16, 17] selected eight fungicides with quite low water solubilities to increase their solubility by complexation with CyDs, and to study the feasibility of preparing solid fungicide@CyD complexes. However, the only two that showed a marked increase of water solubility when complexed with β-CyD were prochloraz (800%) and benalaxyl (440%). The isolation of solid complexes from these fungicides was also possible.

Some hydrophobic organic pesticides have proven to be easily sorbed by soil, decreasing their effectiveness and making it difficult to remove their residues from soils. Agents such as organic co-solvents and surfactants have been considered for improving the solubility of such pesticides, but both present disadvantages from an environmental point of view. As an alternative, CyDs may have potential for use as solubility-enhancement agents. Luo et al. [27] evaluated the ability of β-, HP-β-, and HE-β-CyD to increase the aqueous solubility of methyl parathion, carbofuran, and pentachlorophenol, observing no significant toxicity effect to nontarget organisms, such as tadpoles.

Norflurazon is another herbicide that presents some agricultural and environmental problems, such as prolonged persistence in some kinds of soils, and significant dissipation in the field due to photodegradation and volatilization. Villaverde et al. [14, 28] have studied the possibility of obtaining inclusion complexes with natural CyDs to obtain formulations that improve the behavior of this herbicide in soils. An increase in norflurazon solubility up to five-fold was obtained with α- and β-CyDs and up to four-fold with γ-CyD. Solid complexes were obtained using different processing methods (kneading, spray drying, and vacuum evaporation). Desorption studies of norflurazon from soils in the presence of α- and γ-CyDs showed that both CyDs greatly increased the removal of norflurazon previously adsorbed, proving their potential use for *in situ* remediation of pesticide-contaminated soils [28].

Concern over the contamination of soils and water has led to the development of formulations that prevent entry of the pesticides into the groundwater while main-

taining effective pest control. The release characteristics of guest compounds can be modified by encapsulation of the compounds in CyDs. When complexes are exposed to water, dissolution and release of pesticides occurs. Dailey et al. [29, 30] prepared complexes with selected herbicides (metribuzin, atrazine, alachlor, simazine, and metolachlor) in an attempt to develop formulations that prevent leaching while maintaining effective pest control. β-CyD complexes of atrazine and simazine were prepared only after forcing reaction conditions, but they are impervious to dissociation, owing to their high stability. On the contrary, a metribuzin-β-CyD formulation controlled selected weed species in a greenhouse efficacy study.

Dailey et al. [15] also prepared and characterized β-CyD complexes of the insecticides aldicarb and sulprofos. Groundwater contamination by aldicarb is of particular concern owing to its acute toxicity to mammals; longer residual effects of sulprofos and a reduction in its phytotoxicity and operator hazards were the benefits expected from its complexation with CyDs. Formulations of the β-CyD complex of sulprofos were tested for toxicity against the tobacco budworm on cotton [31]. Although none of the new formulations was as efficacious as the commercial formulation, the addition of additives such as Airvol 205 increased their toxicity against budworm.

Pesticides can be complexed with CyD to reduce their volatility. The interaction of the guest with the CyD produces a higher energy barrier to volatilization. Szente and Szejtli [32] prepared the inclusion complex of the volatile insecticide DDVP with β-CyD obtaining a crystalline substance with a much more persistent contact effect than free DDVP.

Controlled-release solid formulations of selected volatile organophosphorus pesticides (malathion, DDVP, sumithion, chlorpyriphos, and sulprofos) were studied by Szente [33]. These solid formulations exhibited negligible vapor pressure and preserved their entrapped pesticide content even at elevated temperature. Malathion and chlorpyriphos formulations showed increased physical stability, and resulted in an effective masking of the unpleasant smell while the complex formulations existed as dry solid. Sulfluramid is an expensive insecticide that is lost by volatilization, but complexation to β-CyD reduced the loss [21].

When a pesticide is complexed with CyD, the interaction of the side groups on the guest pesticide molecule with the hydroxyl or substituted hydroxyl groups of the host can have an effect on the reactivity of the guest molecule. Depending upon the group on the pesticide molecule, this can result in catalysis of the reaction or stabilization of the guest molecule by prevention of chemical reactions [34]. Studies of the catalytic effects of CyDs on the degradation of pesticides are important for an understanding of their persistence and fate in natural environments, in order to promote the degradation of such hazardous pollutants. Kamiya et al. [35–37] studied the effect of natural and methylated CyDs on the hydrolysis rate of some pesticides. They observed the double merit of β-CyD, which both stabilized the labile parathion, methyl parathion, and fenitrothion and at the same time accelerated the alkaline hydrolysis of paraoxon, which is much more toxic and is produced by the oxidation of parathion in natural environments. This behavior was

explained in terms of the geometry of the inclusion complexes which determine the degree of proximity between the pesticide reaction site and the CyD catalytic site. This work also revealed that methylation of the catalytically active secondary hydroxyl groups of the CyD hosts altered the stabilizing effect.

Ishiwata and Kamiya [38] observed the promotive inclusion-catalytic effect of α-, β-, and γ-CyDs on the degradation of eight organophosphorus pesticides in neutral aqueous media. Pesticide degradations were particularly accelerated in diazinon @α-CyD and chloropyrifos@β-CyD.

Pospisil et al. studied the reduction mechanism of the pesticide vinclozoline in a nonaqueous environment in the presence of β-CyD [39], which changed it from the predominant formation of 3,5-dichloroaniline to the formation of dechlorinated products. These authors had previously demonstrated that the redox properties of the fungicide difenzoquat were also affected by stronger complexation of its reduction product in the presence of β-CyD [7]. In the case of atrazine, which forms complexes with all three natural CyDs, its inclusion into the host cavity enables its reduction even in the non-protonized form [40].

Similarly to CyD complexes with drugs, these hosts can also be used to stabilize unstable pesticide molecules to prevent their interaction and reaction with other molecules, ions, or radicals, since the pesticide is isolated from them. Association with the cavity, or with the hydroxyl groups surrounding the cavity, can also stabilize the guest in less reactive forms. Some pesticides exhibit an increase or decrease in the intensity of light absorption when included in the CyD cavity. Kamiya et al. [35, 42] studied the inclusion effects of α-, β-, γ-, hexa-2,6-dimethyl α- and hepta-2,6-dimethyl-β-CyDs ▌AQ16.3.3▌ on the photodegradation rates of the pesticide parathion and its oxidation product paraoxon. Some of the CyDs promoted the photodegradation of the pesticides, while the others inhibited it. These different effects were related to the inclusion depth parameters of the pesticides into their cavity. The inhibition effect may be caused by too deep inclusion of the phosphorus atom, the reaction centre of the pesticides, which prevent it from interacting with the catalytic sites of the host cavity (the secondary hydroxyl groups) and the water or oxygen molecules from the solvent.

On the other hand, Kamiya et al. [43] observed an increased photodegradation of eleven organophosphorus pesticides in humic water after complexation to α-, β-, and γ-CyDs. They concluded that the promotion effects of CyDs towards photodegradation were attributable to their inclusion-trapping abilities, which are active not only to the pesticides, but also to photoradical species, such as superoxide and hydroxyl radicals, discharged by the photosensitization action of humic acids.

An enhancement of biological activity of some pesticides can also take place as a consequence of the synergistic activity of CyDs, as shown in the case of benomyl [44]. The effectiveness of isoxaben, a benzamide herbicide, is enhanced by CyDs, the growth of *Amarantus retroflexus* and *Solanum nigrum* being inhibited more than by isoxaben alone [45]. Glyphosate formulations with these oligosaccharides enhance plant penetration of the herbicide [46], and aqueous formulations are storage stable and easily diluted with water.

Another advantage of pesticides@CyD complexes is the masking of undesirable effects of the guest molecule. The irritating or toxic effects of some pesticides can be reduced or eliminated. When a guest is included in a molecule of CyD, it is isolated and prevented from coming into contact with body surfaces where it could cause unwanted side effects such as irritation. Loukas et al. [47] prepared γ-CyD complexes of the insecticide DCPE and observed a decrease of its acute oral toxicity, indicating that a safer product for the applicator had been prepared.

The application of CyDs to obtain new formulations of pesticides leads to the presence of CyDs in soils, but little is so far known about their effects on soil physicochemical properties. Jozefaciuk et al. [48] studied the effect of applications of a randomly methylated β-CyD (RAMEB) on three typical clay minerals present in soils, bentonite, illite, and kaolinite, selected as a rational base for understanding soil processes. Their findings suggested that the surface properties and pore structure of minerals changed dramatically when CyDs were introduced, leading to a decrease in surface area, an increase in adsorption energy, and decreases in the volumes of micro and mesopores. These authors also observed a great modification of physical properties in some selected soils after RAMEB addition, such as increasing water adsorption and surface area in sandy soils and their decreasing in clay soils, and an increasing proportion of coarse-size soil fractions owing to aggregation of smaller particles [49]. However, it has not been determined if certain surface and pore properties return to the original state after the removal of the CyD, either by leaching or by biodegradation, or if the phenomena observed for RAMEB are generally true for other CyDs. It was also observed very early in the 1950s that, probably due in part to these changes in soil properties, crop yield increased when β-CyD was used, although the germination process and development of shoots and roots was initially retarded strongly, allowing protection against the influence of herbicides administrated during the sowing.

On the other hand, the inclusion effects of CyDs on certain pesticides could also be influenced by the presence of different soil components. Ishiwata and Kamiya [51] studied the concentration effects of humic acids on the inclusion of organophosphorus pesticides (parathion, methyl parathion, paraoxon) by CyDs. They found that humic acids exert characteristic inhibition effects on the pesticide inclusion to CyDs, which correlate with the inclusion-depth parameters of the pesticide@CyD complexes. These effects can be explained in terms of the complexation and thus solubilization functions associated with humic materials, and may be considered as one of the potential factors to affect the inclusion functions of CyDs applied to control hazardous pollutants in water–soil environments rich in humic substances.

In spite of the relatively large number of papers published on the preparation, characterization, and properties of a wide variety of pesticide@CyD complexes, very few patents exist relating to their real application in the development of pesticide formulations. Most of them are Japanese, although German and Chinese patents can be also found. Some of them are related to the increasing stability of the new pesticide formulations [52–55]. The acaricide amitraz was stabilized by con-

version into an inclusion complex with β-CyD [56], and microcapsules of the pesticide fenitrothion, among others, were prepared using a water-soluble coating material (α-CyD) to obtain stabilized microcapsules that could be easily handled [57].

Some patents refer to the controlled release of certain pesticides [58, 59]. Matolcsi et al. [60] used β-CyD to prepare inclusion compounds with benzenesulfonylurea derivatives with herbicidal or plant growth regulator properties [61], obtaining a prolonged controlled release of the active ingredient. Ikeuchi et al. [62] prepared inclusion complexes of triazole derivatives which presented potent insecticidal activities at low concentrations for an extended period.

Pesticidal compositions containing CyDs to increase their solubility have also been patented [63]. Azadirachtin, a biopesticide of plant origin, highly unstable in aqueous media and extremely sensitive to sunlight, has been formulated using β- and β-methyl-CyD to enhance its solubility [64], avoiding the use of surfactants and organic solvents, which do not sufficiently enhance the shelf life of the formulations.

There are some other patents in which the use of CyD gives an increased efficacy of the pesticide [46, 65, 66]. Xiao and Wang [67] use CyD as a synergist to prepare floating-type agrochemicals for rice fields. Enhancement of the activity of benzamide herbicides has been obtained with CyDs [45]. The association of isoxaben with at least one CyD improved its mobility in the ground and its biological efficacy against dicotyledons in maize and winter cereals and in ornamental trees, especially conifers. Aven et al. [68] have observed a greater degree of enhancement of the herbicidal efficacy of certain herbicides by addition of a larger content of α-, β-, and/or γ-CyDs in the formulation's solid carrier. The addition of CyDs can reduce the recommended amount of active ingredient per hectare, so that additional weeds can be controlled.

Conclusions

This section amply demonstrates the possibility of preparing cyclodextrin inclusion complexes with a wide variety of pesticides, that possess particularly advantageous properties for some specific applications. These complexes would improve the behavior of the pesticides in comparison to the current commercial formulations, but, according to Szejtli [69], the pesticide industry is very raw-material price sensitive, and it seems that up to now the price of even the cheapest technical-quality β-CyD is too high to allow the commercialization of these pesticide formulations.

Although most of the pesticides@CyD inclusion complexes studied have used β-CyD because of its lower price, there are also advantages to other CyDs, depending on a proper fit of the pesticide molecule into the hydrophobic CyD cavity. Although most of the published papers related to pesticides are not directly practice-oriented, a wide variety of CyD derivatives have been studied as hosts for pesticides at the laboratory scale. For the same reason, many different processing methods, some of them highly sophisticated, have been used to prepare pesticides@CyD inclusion

complexes, even though there was no possibility of using them to prepare pesticide formulations on an industrial scale.

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