

## Characterization of Inclusion Complexation between Fenoxaprop-*p*-ethyl and Cyclodextrin

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Cyclodextrins (CDs) derived from natural starches are capable of forming inclusion complexes with a variety of organic compounds. This work evaluated the complexation role of CDs toward fenoxaprop-*p*-ethyl (FE) in an attempt to assess their potential as new formulation additives for more efficient FE delivery and better environmental approaches.  $\beta$ -CD and its two derivatives, randomly methylated  $\beta$ -CD (RAMEB) and 2-hydroxypropyl  $\beta$ -CD (HP- $\beta$ -CD), were tested. The solubility of FE was enhanced in the presence of the CDs due to the formation of inclusion complexes, with RAMEB being >6 times more effective than the other two. The complexation was confirmed by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD), where the FE melting peaks in DSC, the FTIR bands, and the XRD peaks were generally weakened. Within the tested time up to 60 min, the dissolution of the FE-CD complexes resulted in higher FE concentrations than did that of FE by itself. The dissolution of the FE-RAMEB complex was much faster than other complexes and FE alone. These results indicate that RAMEB was a better inclusion complexation agent for FE in terms of both solubility enhancement and dissolution rate. RAMEB may thus be used to improve FE delivery and to mobilize FE in soil for bioremediation.

**KEYWORDS:** Fenoxaprop-*p*-ethyl; cyclodextrins; inclusion complex; solubility; dissolution

### INTRODUCTION

Cyclodextrins (CDs), a class of natural cyclic oligosaccharides, are composed of six or more  $\alpha$ -(1,4)-linked glucose units forming a toroidal shape with a hydrophobic cavity (1). Primary and secondary hydroxyl groups are present on the smaller and larger rims, respectively, making the external surface hydrophilic. CDs are capable of forming inclusion complexes with a large number of guest molecules of appropriate size and polarity (2–5). The complexation with CDs usually increases the water solubility of the guest molecule (6–8). CDs are thus often used to enhance the solubility of, for example, pesticides for agricultural and environmental applications (9, 10). However, direct use of CDs,  $\beta$ -cyclodextrin ( $\beta$ -CD) in particular, is often limited due to their limited water solubilities (11). On the other hand, randomly methylated  $\beta$ -CD (RAMEB) and 2-hydroxypropyl  $\beta$ -CD (HP- $\beta$ -CD), both being the mixtures of isomers with different degrees and patterns of substitution, are most commonly used to enhance solubility and in turn the bioavailability of low-polarity compounds, as they are comparatively soluble in water and easily produced in comparison to other CD derivatives (12, 13). Furthermore, RAMEB and HP- $\beta$ -CD

are nontoxic, readily cometabolized with herbicides by microorganisms, and thus nonpolluting to the environment (14–16).

Pesticide contamination has been a constant environmental concern. Safe use of pesticides depends on the physicochemical properties of not only the pesticides but also the formulation of additives. The capability of CDs forming inclusion complexes with pesticides offers advantages over conventional formulation additives in reducing pesticide contamination. The potential roles of CDs include reducing mammalian toxicity, decreasing phytotoxicity to plants (17–19), masking bad odors, providing catalytic effects on the degradation of pesticides (20), and so forth. CDs are commercially available in large quantities and at a price affordable for agricultural applications and environmental remediation (21). A steady increase in the application of CDs to pesticide formulations and contamination reduction is thus predicted soon.

Fenoxaprop-*p*-ethyl (FE) is a postemergence systemic broad-spectrum gramineous herbicide and was first registered in Germany by Hoechst AG in the 1970s. It belongs to the racemate 2-(4-aryloxy phenoxy) propionic acid herbicide group and inhibits biosynthesis of aliphatic acid compounds (22). It is used to destroy and prevent grassy weeds in beets, cotton, flax, peanut, cole, potato, soybeans, wheat, and rye. Following field selection for several consecutive years in Europe and North America, some grasses have gradually developed resistance to FE (23, 24). As there is no obvious evidence of the resistance

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in China, FE remains widely used to control germinating grasses across the country. FE has a water solubility of  $\sim 2.0 \times 10^{-3}$  mM at 20 °C and is hydrophobic in nature with a log  $K_{OW}$  value of 4.95. It rapidly hydrolyzes to fenoxaprop acid, the principal herbicidal form with a hydrophilic nature (25). However, hydrolysis must be inhibited first by means of emulsification or complexation for FE to effectively penetrate into weed cells through surface cuticles.

Current commercial FE is formulated and sold as an emulsifiable concentrate. Enhanced solubilization by complexation may increase FE efficiency and prevent overdosing for more cost-effective agricultural practices and better environmental approaches. In this study, the role of  $\beta$ -CD, RAMEB, and HP- $\beta$ -CD as inclusion complexation agents for FE was evaluated. This was accomplished by measuring the solubility of FE in the presence of the respective agents. The solid complexes were prepared, and their dissolution rates were determined. The complexes were extensively characterized by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and X-ray powder diffraction (XRD) techniques. The study was conducted, in terms of FE delivery, as well as its degradation, leaching, and/or stability in soil, in an attempt to identify the most appropriate complexation agent among the three CDs as potential formulation additives for FE.

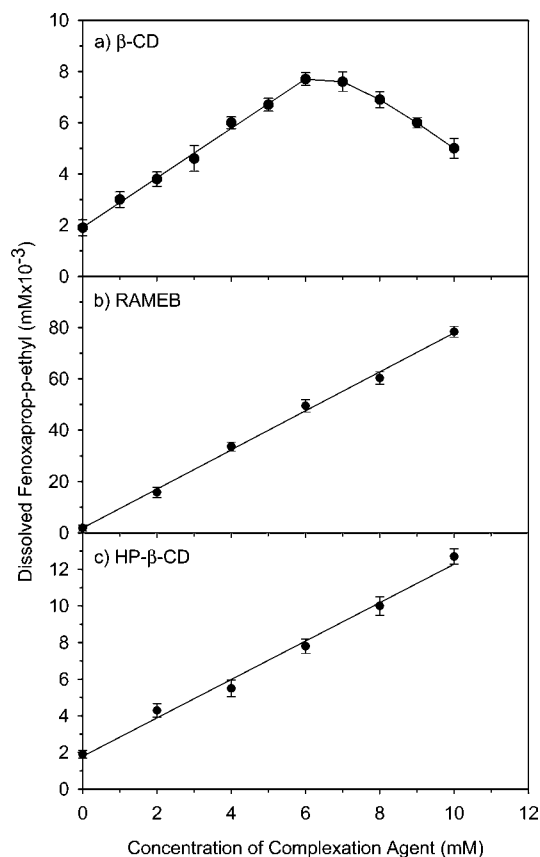
## MATERIALS AND METHODS

**Chemicals.** Fenoxaprop-*p*-ethyl (purity of 95.0%) was kindly supplied by Anhui Huaxing Co. Ltd. (Anhui, China).  $\beta$ -CD (purity of 99%) and HP- $\beta$ -CD (average degree of substitution was 0.6) were purchased from Shanghai Bio Life Science and Technology Co. Ltd. and Shaanxi Liqian Chemical Industrial Co. Ltd., respectively. RAMEB was synthesized in our laboratory according to the reported procedures (26). The average degree of substitution of RAMEB was 1.8 per anhydroglucose unit. Methanol was of HPLC grade, and water was deionized. All other chemicals were of analytical reagent grade and used as received.

**Phase Solubility.** The phase solubility measurements were performed according to the method of Higuchi and Connors (27). Excess FE (2 mg) was added to a glass bottle containing 10 mL of deionized water (pH 6) and various amounts of  $\beta$ -CD, RAMEB, or HP- $\beta$ -CD. All the measurements were in triplicate. Solutions were shaken at 25 °C for 120 h. Preliminary experiments indicated that 120 h shaking was sufficient for the dissolution to reach equilibrium. After the establishment of equilibrium, the content of each bottle was filtered through a 0.45  $\mu$ m Millipore membrane. The first 2 mL of the filtrate was discarded to avoid any potential loss of FE to adsorption by the filter. The remaining filtrate was collected for the analysis of FE.

**HPLC.** The analyses were performed using an LC-10ADvp HPLC (Shimadzu, Kyoto, Japan) equipped with a SPD-10Avp photodiode array detector, a SIL-10ADvp automatic injector, two HPLC pumps, a CTO-10Avp oven, and the Class-vp data system. Prior to analysis, samples were appropriately diluted with water to ensure that the concentration of FE was within the linear detection range. The column was a YMG C18 (250  $\times$  2.5 mm (i.d.)) column and was maintained at 40 °C during analysis. The mobile phase was a mixture of methanol and water (80:20, v/v) with a flow rate of 1.0 mL min<sup>-1</sup>. The detection wavelength was set at 230 nm, at which there was no obvious interference from  $\beta$ -CD, RAMEB, or HP- $\beta$ -CD. The FE-CD complexes readily dissociated in the mobile phase, and total dissolved FE was thus determined.

**Inclusion Complexes.** The inclusion complexes of FE and  $\beta$ -CD, RAMEB, or HP- $\beta$ -CD (expressed as FE- $\beta$ -CD, FE-RAMEB, or FE-HP- $\beta$ -CD) were prepared by the kneading method (6). According to phase solubility, the complexes had a 1:1 (FE/CD) stoichiometry (described in the Results and Discussion). Equimolar FE and each of the CDs were mixed in a mortar and kneaded for 45 min. During the kneading, 2 mL of ethanol was added to the mixture to maintain a proper consistency. The product was dried at 37 °C for 48 h and gently



**Figure 1.** Solubility of FE in the presence of (a)  $\beta$ -CD, (b) RAMEB, and (c) HP- $\beta$ -CD.

ground to powder  $<125 \mu$ m. As controls, physical mixtures of equimolar FE and the corresponding CDs were also prepared by dry-pestling in a mortar for 5 min (expressed as FE +  $\beta$ -CD, FE + RAMEB, and FE + HP- $\beta$ -CD).

**DSC.** DSC was performed using a DSC Q100 V 7.3 Build 249. Samples of about 6 mg were placed in closed aluminum pans in N<sub>2</sub> gas flow. The heating rate was 10 K min<sup>-1</sup> over the temperature range from 310 to 570 K.

**FTIR.** The FTIR spectra were obtained using a Shimadzu 8900 FTIR spectrometer (Kyoto, Japan) with 4 cm<sup>-1</sup> resolution and 64 scans between wavenumbers of 400 and 2000 cm<sup>-1</sup>. Samples were prepared as KBr disks with 1 mg of complex in 100 mg of KBr.

**XRD.** The X-ray powder diffraction patterns were recorded using an X-ray diffractometer D/max-rA equipped with CuK $\alpha$  radiation at 40 kV and 80 mA, from 5 to 70° 2 $\theta$ , in steps of 0.02° 2 $\theta$  and 1° 2 $\theta$  min<sup>-1</sup>.

**Dissolution Rates.** The dissolution rates were determined at 37  $\pm$  0.5 °C using the paddle method. FE, physical mixture, or inclusion complex (3 mg) was placed in 1 L of deionized water and continuously stirred at 50 rpm on a magnetic stirrer. At various times up to 60 min, the concentration of FE was measured by HPLC. All measurements were in triplicate.

## RESULTS AND DISCUSSION

**Phase Solubility.** The phase solubility diagram of FE and  $\beta$ -CD shown in Figure 1a is classified as type B<sub>s</sub>, according to Higuchi and Connors (27). Three regions can be identified in the diagram. There was an initial increase in FE solubility (CD concentration  $<6$  mM) due to the formation of a more soluble inclusion complex. The linearity of this line segment indicates a 1:1 stoichiometry in the complex. The solubility plateau over the intermediate CD concentration range (between 6 and 7 mM) was a result of a dynamic mass balance between continued FE dissolution and the precipitation of its complex. The latter may

have resulted from the low solubility of  $\beta$ -CD, with the FE- $\beta$ -CD complex being preferentially precipitated. A further increase in the concentration of  $\beta$ -CD (>7 mM) resulted in an increased precipitation of FE- $\beta$ -CD and hence a decreased FE solubility. The measured maximum apparent solubility of FE in the presence of  $\beta$ -CD was about 4 times that in the absence of CD, demonstrating its ability as an inclusion complexation agent for the enhancement of FE solubility.

The apparent stability constant,  $K_c$ , of FE- $\beta$ -CD can be calculated from the slope and intercept of the linear segment of the phase solubility line (the concentration of  $\beta$ -CD <6 mM), according to the following equation (27):

$$K_c = k/S_0(1 - k)$$

where  $S_0$  is the intrinsic solubility of FE in deionized water and  $k$  is the slope of the straight line. The calculated apparent stability constant of FE- $\beta$ -CD was 502.7 M<sup>-1</sup>.

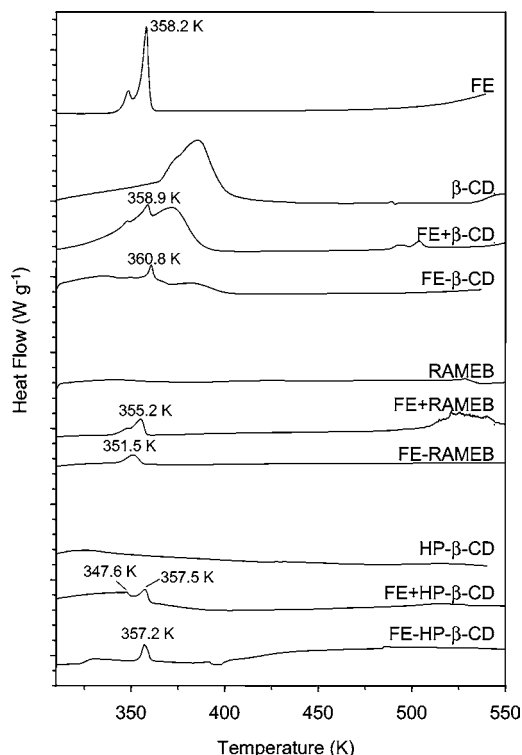
The apparent solubilities of FE in the presence of RAMEB and HP- $\beta$ -CD are presented in **Figure 1b,c**, respectively. Both lines are linear without leveling off with a slope <1. These lines are classified as type  $A_L$  (27) and indicate the formation of 1:1 complexes between FE and respective CDs. The calculated apparent stability constants were 4172.3 and 590.5 M<sup>-1</sup> for FE-RAMEB and FE-HP- $\beta$ -CD, respectively.

Comparison of the calculated apparent stability constants reveals that RAMEB had the greatest ability to form a complex with FE. This may be understood on the basis that RAMEB contains methoxy groups, which decrease the polarity of the lips of the cavity. This structural feature is in favor of hydrophobic interactions, via which FE presumably penetrated deeply into the cavity (1). The comparatively lower complexation ability of  $\beta$ -CD and HP- $\beta$ -CD may be due to the hindrance on the FE penetration by more hydrophilic hydroxyl groups (7). In this regard, RAMEB is considered to be a preferred solubility enhancement agent for FE.

**DSC.** The DSC thermogram of FE from 310 to 550 K showed a sharp endothermic peak at 358.2 K (**Figure 2**), corresponding to its melting point (22). For  $\beta$ -CD, a broad endothermic peak was recorded over the range of 363–413 K, which may be due to its dehydration. The physical mixture of FE and  $\beta$ -CD showed two partially overlapped but clearly visible peaks corresponding to FE melting and dehydration of  $\beta$ -CD, respectively, suggesting little, if any, direct interaction between the two components. Much diminished peaks with the kneaded sample apparently were due to the formation of the FE- $\beta$ -CD complex, in which the water molecules originally residing in or near the cavity were partially displaced by FE.

The thermogram of RAMEB did not show any obvious endothermic peaks over the tested temperature range (310–550 K). The lack of dehydration demonstrated the hydrophobicity of RAMEB. It also suggested the amorphous character of the sample, as verified later by XRD. The physical mixture of FE and RAMEB thus showed only the FE melting peak. The slightly lower melting point may indicate a small amount of the FE-RAMEB complex formed during mixing. For the kneaded sample, the decrease in the peak intensity was due to the formation of the FE-RAMEB complex. The obvious peak shift to a lower melting point may be ascribed to the effective complexation of FE and its possible crystal transition or the formation of a new crystal structure in the cavity of RAMEB (6), although the exact mechanism remains to be understood.

A small broad endothermic peak within the range of 310–350 K with HP- $\beta$ -CD was noticed. This can be ascribed to dehydration, although the amount of water associated with the



**Figure 2.** DSC thermograms of FE,  $\beta$ -CD, RAMEB, and HP- $\beta$ -CD, as well as their physical mixtures and complexes.

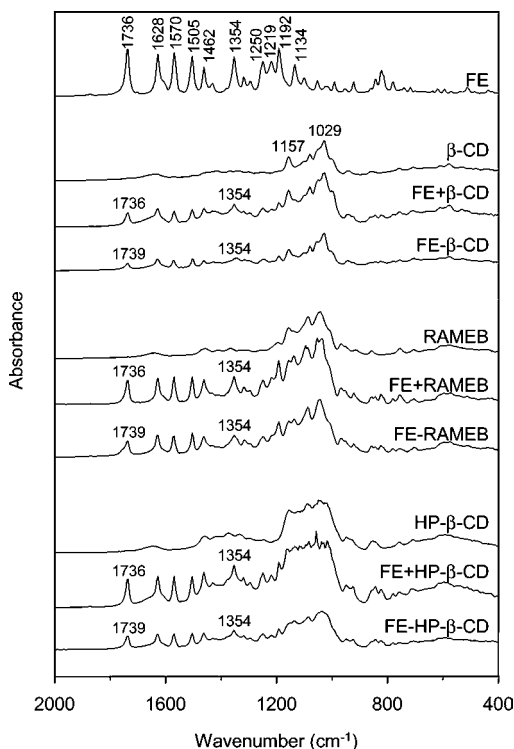
hydroxyl groups in HP- $\beta$ -CD appeared insubstantial. The physical mixture of FE and HP- $\beta$ -CD showed both the melting peak of FE and the dehydration peak of HP- $\beta$ -CD. The FE melting peak intensified, and the dehydration peak disappeared for the kneaded sample, strongly suggesting the formation of a FE-HP- $\beta$ -CD complex (7).

The previous observations suggest the complexation between FE and  $\beta$ -CD, RAMEB, as well as HP- $\beta$ -CD during kneading but little in physical mixing. The largest change in the thermogram was with kneaded FE-RAMEB, in which the melting point of FE was shifted significantly lower. This is in agreement with the phase solubility determination that RAMEB had a much higher ability to enhance the solubility of FE than the other two CDs.

**FTIR.** The complexation between FE and CDs was further evidenced by the FTIR data in **Figure 3**. Several principal bands for FE were observed between wavenumbers of 2000–400 cm<sup>-1</sup>. The intensive bands at 1736 and 1354 cm<sup>-1</sup> were assigned to the C=O stretching and the methyl C-H bending, respectively. Other bands include those at 1192 and 1134 cm<sup>-1</sup> assigned to the respective asymmetric and symmetric C-O-C stretching for the propanoate fragment at 1628, 1570, 1505, and 1462 cm<sup>-1</sup> to the aromatic ring vibration, as well as at 1250 and 1219 cm<sup>-1</sup> to the aromatic Ar-O-C stretching.

The spectrum of  $\beta$ -CD displayed several intensive bands within the range of 1029–1157 cm<sup>-1</sup>, which are assigned to the primary and secondary C-OH stretching. The bands of RAMEB and HP- $\beta$ -CD were noticeably different from those of  $\beta$ -CD. It was difficult to elaborate on the difference, as both CDs were mixtures of isomers with various degrees and patterns of substitution.

The physical mixtures of FE and CDs showed weakened characteristic bands of FE in the respective mixture spectra. This was due presumably to the dilution of FE. By comparison, the bands with the kneaded samples characteristic of the FE aromatic ring vibration (at 1628, 1570, 1505, and 1462 cm<sup>-1</sup>)

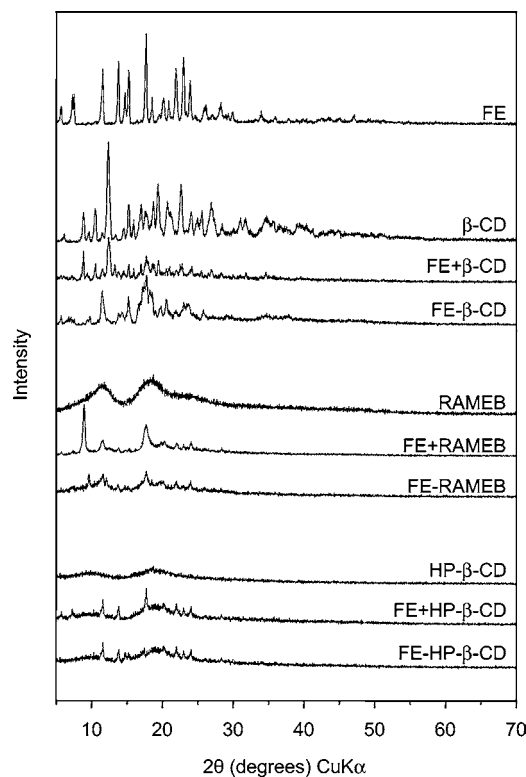


**Figure 3.** FTIR spectra of FE,  $\beta$ -CD, RAMEB, and HP- $\beta$ -CD, as well as their physical mixtures and complexes.

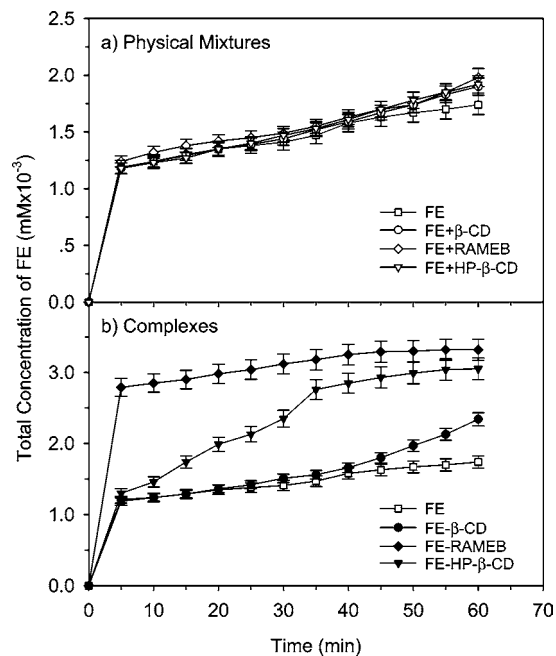
were further weakened, suggestive of the formation of complexes in these samples. Furthermore, the band characteristic of the FE carbonyl stretching was shifted to  $1739\text{ cm}^{-1}$ . This suggests that hydrogen bonding between the carbonyl of FE and the hydroxyl of CDs has most likely contributed to the formation of complexes in the cavity of CDs.

**XRD.** Additional evidence of the complexation was derived from the X-ray powder diffraction shown in **Figure 4**. Sharp peaks over the diffraction angles indicate the crystal nature of FE and  $\beta$ -CD. In contrast, both RAMEB and HP- $\beta$ -CD lost the nature of  $\beta$ -CD and became amorphous. The physical mixture of FE and  $\beta$ -CD showed sharp peaks, most of which corresponded to those in their individual patterns. The peaks in the kneaded sample became less sharp, and a few new peaks (e.g.,  $11.54$ ,  $18.22$ ,  $23.04$ , and  $23.70^\circ 2\theta$ ) appeared, suggesting the formation of the FE- $\beta$ -CD complex. The physical mixture of FE and RAMEB remained somewhat amorphous due to the nature of RAMEB but also retained a few diffraction peaks of FE. One distinguishable new peak ( $8.96^\circ 2\theta$ ) suggested some interactions between FE and RAMEB, for reasons discussed earlier. The kneaded sample was mostly amorphous. The loss of the FE crystal nature was ascribed to the formation of the FE-RAMEB complex. Similar observations with FE and HP- $\beta$ -CD are again suggestive of the formation of the FE-HP- $\beta$ -CD complex.

**Dissolution Rates.** FE dissolved rapidly in water (**Figure 5**). At 5 min, the measured FE concentration was  $1.2 \times 10^{-3}$  mM, about 60% of its intrinsic solubility. The dissolved FE concentration then slowly increased with time. The presence of CDs increased neither the dissolution rates nor the dissolved concentrations of FE in the physical mixtures (**Figure 5a**), resulting apparently from the lack of the FE-CD complexation in these samples. It also indicated that little dissolved FE was complexed by the CDs in solutions within the tested time (<60 min). The in-solution complexation would otherwise have enhanced the dissolved FE concentration. In contrast, the FE-



**Figure 4.** XRD of FE,  $\beta$ -CD, RAMEB, and HP- $\beta$ -CD, as well as their physical mixtures and complexes.



**Figure 5.** Dissolution of FE and its physical mixtures and complexes with  $\beta$ -CD, RAMEB, and HP- $\beta$ -CD.

RAMEB dissolved much faster than FE. The measured dissolved FE concentration reached  $2.8 \times 10^{-3}$  mM at 5 min and continued to increase with time (**Figure 5b**). By comparison, the dissolution of FE-HP- $\beta$ -CD was much slower, although it remained constantly higher than that of FE alone. The dissolution of FE- $\beta$ -CD was similar to or only slightly higher than that of FE. RAMEB apparently provided the best performance in facilitating the dissolution of FE.

**Conclusions.** Cyclodextrins (CDs) may be used as potential formulation additives for fenoxaprop-*p*-ethyl (FE), as they are

inexpensive and environmentally safer than the conventional additives. They are capable of forming complexes with FE, thus not only enhancing the solubility of FE for more efficient delivery but also preventing its hydrolysis to facilitate its penetration into plant cells. The complexation between FE and CDs can be identified by the techniques including differential scanning calorimetry, Fourier transform infrared spectroscopy, and X-ray diffraction, as used in this study. Among the tested CDs, randomly methylated  $\beta$ -CD (RAMEB) appears to be a better complexation agent for FE than  $\beta$ -CD and 2-hydroxypropyl  $\beta$ -CD (HP- $\beta$ -CD), as the FE-RAMEB complex has a higher stability constant and solubility and dissolves faster. In regard to its complexation ability, RAMEB may also be used to mobilize FE in soil to increase its availability to microorganisms for enhanced bioremediation.

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