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ORIGINAL ARTICLE

Formation of inclusion complexes and controlled release of atrazine using free or silica-anchored β-cyclodextrin

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Abstract Immobilization of cyclodextrin on the surface of silica was performed using citric acid as the bonding agent. Inclusion complexes of atrazine with free (CD) or anchored (CDSI) β-cyclodextrin were prepared and then characterized using infrared spectroscopy, X-ray diffraction and differential scanning calorimetry. The complexation reaction showed first order kinetics, with a rate constant (k) of 8.72×10^{-3} min^{-1}. There was a rapid increase of absorbance in the first 40 min, followed by attainment of equilibrium after ~2 h. The stoichiometry of the reaction was 1:1, with both free and anchored β-cyclodextrin increasing the solubilization of atrazine in an aqueous medium (by around 1.5 and 3.4 times, respectively). The association constant (K_a) of the complex was 28.93 L mol^{-1} using CD and 130.68 L mol^{-1} using CDSI. In release tests, 62% of the atrazine complexed with CDSI or β-CD was released after 40 h, while 83% of free atrazine was released during the same period.

Keywords Cyclodextrin · Silica · Functionalization · Inclusion complex · Herbicide · Controlled release

Introduction

The use of herbicides and other chemical agents in agriculture has become ubiquitous due to the need to feed a growing population that is expected to reach nine billion in 2050 [1]. In recent years, few countries have matched Brazil's growth in terms of international agri-business. The increased productivity of Brazilian agriculture has been due, in large part, to the introduction of new technologies and materials, including the use of agrochemicals. As a result, Brazil is now one of the world's major consumers of these products [2].

A difficulty associated with the use of agrochemicals is that a large proportion fails to reach its target. Around 90% of the pesticide applied is lost through evaporation, leaching, run-off or biological degradation. Such losses result in the use of unnecessarily large quantities of chemicals to control pests and diseases [3, 4].

Atrazine (ATZ) (Fig. 1a) is a selective herbicide employed to control weeds in plantations of maize, sugar cane and soya. It is classified as a selective systemic herbicide for the pre- and post-emergent control of broad-leaved plants [5]. Its action is based on inhibition of photosynthesis by interruption of the Hill reaction [6]. The widespread use of ATZ and its high mobility in soils has resulted in its presence in surface and subterranean waters at levels exceeding permissible limits [7]. The half-life of ATZ can vary between around 2 months and 6 years, depending on environmental conditions. Studies have shown that this substance can interfere in the normal functioning of the endocrine systems of animals including humans [8].

Natural adsorption by soils can reduce the losses of pesticides. This process involves surface adsorption followed by slow diffusion of the chemical within soil aggregates. However, rainfall occurring close to the time of application can result in the pesticide moving freely in solution within the soil, without coming into contact with adsorption sites [9].

Techniques that enhance adsorption can help to reduce transport losses and hence mitigate environmental

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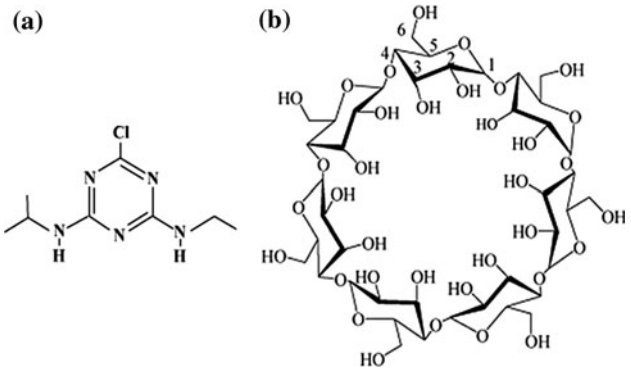

Fig. 1 Chemical structures of **a** atrazine and **b** β-cyclodextrin, composed of seven glucose monomers

contamination. This is the principle underlying the use of controlled release formulations, which have become increasingly popular in the agrochemical industry in recent years. The use of such formulations can also help to reduce both the toxicity of the active agent and the exposure of workers to pesticides. In these products, the active ingredient is encapsulated within an inert matrix, so that only a fraction is immediately available, with the remainder being released slowly over time at a rate that is determined by the mechanism involved [10].

Controlled release of agrochemicals such as atrazine influences the rate at which they reach their targets and can lower the dosages required. This can reduce toxicity and environmental impacts, while at the same time providing farmers with more effective techniques for the control of pests and diseases. Furthermore, reducing the quantity of pesticides used in agriculture makes better economic sense than attempting to degrade these chemicals into less toxic forms. The adoption of controlled release technologies could be an important means of reducing environmental pollution. They contribute to the aims of sustainable development, since they improve the mode of action of pesticides, increasing their durability, reducing the amounts required and minimizing impacts on soil microbes.

Cyclodextrins (CDs) have shown potential for use as systems for the modified release of agrochemicals. The structures of these agents include primary and secondary hydroxyl groups that are directed outwards (Fig. 1b). The exterior is therefore hydrophilic, while the internal cavity is hydrophobic, enabling the CDs to form molecular inclusion complexes. This alters the physico-chemical properties of the included molecules in terms of their solubility in water, stability and availability [11].

CD inclusion complexes have potential uses in the food, pharmaceutical, fermentation and fine chemical industries for the preparation, separation and purification of products such as fragrances, drugs and pesticides, as well as for the encapsulation and controlled release of these substances [12–14]. The CDs can be immobilized on a diverse range of supports, including magnetic and polymeric materials, which can further improve their properties for use in specific applications [15].

The presence of silanol groups on the surface of silica enables its chemical modification [16] to produce versatile new materials whose specific properties are determined by the species bound to the surface and which can be used in a wide variety of technological applications. One of the most commonly used techniques to modify silica employs reaction with silylation agents (organosilanes) to form inorganic–organic hybrid compounds [17]. The low Lewis acidity of the silicon atom results in non-polar bonding with carbon, so that the silanes are highly efficient in providing the link between the organic agent and the inorganic oxide support. This link is only possible because of the reactivity of the alkoxide groups towards the silanols present on the silica surface [16, 18].

The combination of the properties of the CDs and silica offers innumerable possibilities for the modified release of agrochemicals. Due to the agricultural importance of atrazine, it is essential to develop techniques for its application that can provide benefits such as improved solubility as well as reduced phytotoxicity, photodegradation and environmental contamination. The objective of this work was therefore to prepare and evaluate inclusion complexes between ATZ and β-CD, either free or anchored on silica gel (CDSI), which might be able to offer such benefits.

Materials and methods

Functionalization of silica with CD

The β-CD used in this study was obtained from Cavamax. Silica gel (60 G, pore volume 0.65–0.85 mL g^{-1}, specific surface area 350–450 m^2 g^{-1}), citric acid (99.5% purity) and xylol were obtained from Vetec.

Anchoring of the CD on the silica surface was performed by adding 2 g of silica, citric acid and β-CD to 50 mL of xylol, followed by refluxing for 6 h. The product (CDSI) was filtered, washed abundantly with distilled water (under vacuum), dried in a drying cabinet for 48 h at 55 °C to eliminate the solvent, macerated and finally sieved to obtain a grain size <150 μm.

Preparation of the ATZ/CDSI and ATZ/CD inclusion complexes

The solid complexes were obtained by mixing equimolar quantities of ATZ and either CDSI (considering the amount of CD supported on the silica) or β-CD. The ATZ was dissolved in a solution of acetone and water (4:1), after which the CDSI or β-CD was added and the system

maintained under agitation for 12 h. The solvent was eliminated at 100 rpm and 50 °C using a rotary evaporator (Fisatom Model 802). The product obtained was macerated, suspended in ultrapure water (Milli-Q), frozen and then later lyophilized (Labconco Freezone 4.5). The complexes were stored in sealed tubes at −22 °C.

Characterization of the inclusion complexes containing ATZ

Evidence for the formation of the inclusion complexes was obtained by characterization using infrared spectroscopy (FTIR), X-ray diffraction (XRD) and differential scanning calorimetry (DSC).

The FTIR spectra were acquired using a Fourier transform Digilab Excalibur FTS 3000 spectrometer with KBr windows. 97 mg of KBr and 3 mg of the material to be analyzed were weighed out, dried at 60 °C for 1 h and stored in a desiccator. The material was compressed in a hydraulic press for 10 s at a pressure of 3 tons. The spectra were obtained in the range from 4,000 to 400 cm^{-1}, at a resolution of 8 cm^{-1} and with accumulation of 32 scans.

The XRD measurements were performed using a Philips Model PW 130 generator, operated with a Cu-Kα source at 2θ, in the region between 5 and 40°, with a tube current of 20 mA and voltage of 40 kV.

The DSC analyses employed a Shimadzu Model 60 AH calorimeter. Portions of samples ($\sim$5 mg) were heated at a rate of 10 °C min^{-1}, between 25 and 200 °C, under an atmosphere of N_2.

Kinetics of formation of the inclusion complex between ATZ and β-CD

The kinetics of formation of the inclusion complex between ATZ (provided by Syngenta) and β-CD was studied (in duplicate) by preparing an equimolar solution of ATZ and β-CD in ultrapure water. Following homogenization, measurements were made at predetermined time intervals, using a UV–Vis spectrophotometer (Varian, Model Cary 50 Probe) operated at the maximum absorption wavelength of ATZ (220 nm), until the system reached equilibrium. The order of the reaction and the kinetic constant (k) were determined from the plot of $ln\ A$ (absorbance) against t (time).

Solubility kinetics

Equimolar quantities (1.53 mmol) of ATZ and either CDSI or β-CD were placed in 125 mL Erlenmeyer flasks and agitated for predetermined time intervals up to 24 h. After each time interval, two flasks (duplicates) were removed and the contents centrifuged at 2,500 g for 10 min followed by filtration using 0.22 μm Millex GP membranes (Millipore). The absorbance of the solution was then measured at 220 nm.

Solubility isotherms and determination of the association constant

The solubility studies were performed using the method described by Higuchi and Connors [19]. The isotherms obtained reflect the solubility, which can increase or decrease according to the CD concentration. For a 1:1 complex, the value of the association constant (K_a) can be calculated from the ratio between the slope and intercept of the initial linear portion of the plot [19], as described in Eq. 1

$$K_a = slope / S_0(1 - slope) \quad (1)$$

The experiment (performed in duplicate) consisted of adding different quantities (3, 6, 9, 12, 15 and 18 mM) of CDSI or CD to an excess of ATZ (1.53 mM) in aqueous solution. A control with pure silica was also performed. The mixtures were agitated for 24 h and then centrifuged. The supernatant was removed with the aid of a syringe and filtered using 0.22 μm Millex membranes. The absorbance of ATZ was then measured at 220 nm.

ATZ release experiments

The release tests employed systems consisting of two compartments separated by dialysis membranes (Sigma-Aldrich) with a molecular exclusion pore size of 1,000 Da, enabling observation of the release of ATZ from the donor compartment (volume 5 mL) to the acceptor compartment (volume 100 mL) containing ultrapure water. The system was maintained under constant gentle horizontal agitation and samples were collected from the acceptor compartment over a period of 80 h. The release profiles were obtained by plotting the percentage of ATZ released as a function of time. The experiments were performed in triplicate and the amounts of ATZ released were calculated using the ATZ calibration curves.

Results and discussion

Infrared spectroscopy

The absence of formal bonding between β-CD and ATZ precludes the existence of any major differences (such as band shifting and bending) between the spectra of the inclusion compound and the free compounds. Moreover, the fraction of ATZ contained in the complex was low and

generally did not exceed 20% for β-CD or 10% for CDSI (calculated taking the amount of ATZ used during preparation of the complex as 100%). Bands that might be attributed to vibrations of ATZ were therefore easily obscured by the bands from β-CD or CDSI.

In the present application, this technique was therefore used with the basic objective of identifying the vibrations observed, together with any slight changes in the spectra that could be indicative of inclusion of ATZ within the CD cavity.

No shifts were observed in the absorption minima of the β-CD bands for the inclusion complex formed between ATZ and CDSI (Fig. 2, lines a and b). There were slight shifts in the absorption bands of ATZ for both the physical mixture and the inclusion complex. Singlet absorption at 3,259.6 cm^{-1} is characteristic of secondary amine N–H vibrations. This band was shifted to 3,274.9 cm^{-1} for both the ATZ/CDSI inclusion complex and the physical mixture. Absorption at 1,547.3 cm^{-1} is characteristic of deformation of the C=N bond [20], and this band also showed a shift (to 1,555.7 cm^{-1}) for both the complex and the physical mixture. These slight changes in the spectra are indicative of interactions between ATZ and the CD, suggesting that inclusion in the lyophilized complex had occurred.

In the case of the non-functionalized CD (Fig. 2, lines d and e), shifts occurred in the same bands observed for CDSI, with identical values for the physical mixture and the lyophilized complex: 3,280.5 cm^{-1} for the N–H vibrations band and 1,550.2 cm^{-1} for C=N bond deformation. Suppression of the absorption band at 1,640 cm^{-1}, attributed to angular vibrations of water molecules, together with the slight shifts described above, are indicative of the inclusion of ATZ within the CD during the lyophilization process.

The results provide evidence for the inclusion of ATZ within the CD in the physical mixture. This is of considerable interest for commercial production of inclusion compounds, and has been evaluated for the manufacture of a series of drugs. However, the phenomenon is highly undesirable when the objective is to identify host/guest interactions using mechanical mixtures as comparative parameters.

X-ray diffractometry

The X-ray diffractograms provided evidence for formation of the ATZ/CDSI and ATZ/CD inclusion complexes (Fig. 3). The technique was used in order to identify the occurrence of changes in the crystalline phase that might be indicative of guest inclusion, using the structures of the individual host and guest species as references [21].

There were reductions in the intensities of several peaks for both the inclusion complexes (Fig. 3, lines a and d) and the physical mixtures (Fig. 3, lines b and e). The guest peaks showed slight changes in the presence of CD, while essentially amorphous profiles were obtained in the presence of CDSI.

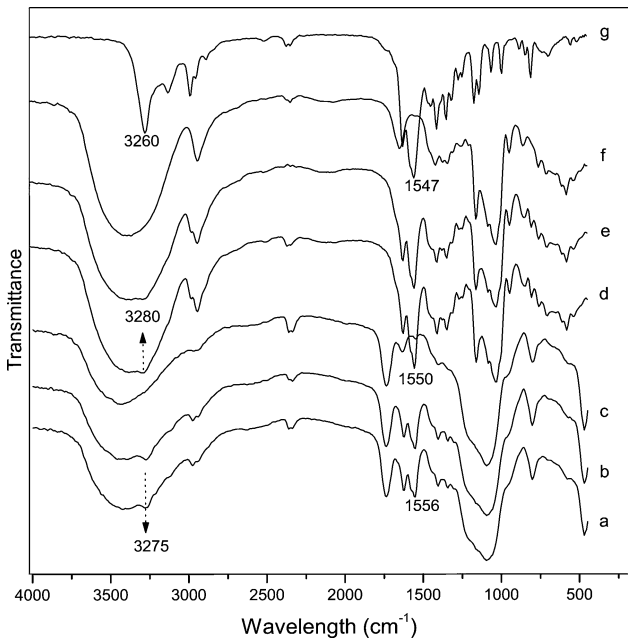

Fig. 2 FTIR spectra obtained for *a* ATZ/CDSI complex, *b* ATZ + CDSI physical mixture, *c* CDSI, *d* ATZ/CD complex, *e* ATZ + CD physical mixture, *f* β-CD; *g* ATZ

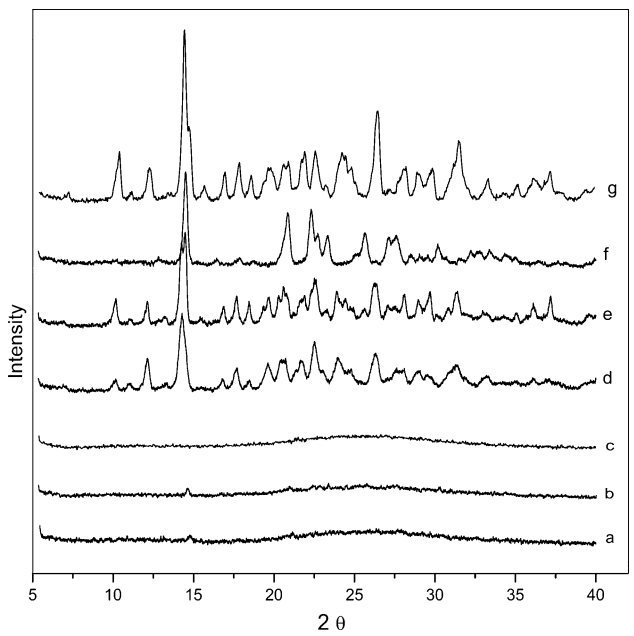

Fig. 3 X-ray diffraction results for *a* ATZ/CDSI complex, *b* ATZ + CDSI physical mixture, *c* CDSI, *d* ATZ/CD complex, *e* ATZ + CD physical mixture, *f* β-CD, *g* ATZ

Differential scanning calorimetry

The DSC analyses were performed for samples consisting of ATZ, ATZ/SI, β-CD, ATZ/CD, CDSI and ATZ/CDSI, as well as the physical mixtures. The thermograms obtained (Fig. 4) revealed endothermic peaks characteristic of the individual components and the inclusion complexes.

A peak at 135 °C in the β-CD thermogram (Fig. 4, line d) was due to the loss of cavity solvation water [22]. In the case of the ATZ/CD complex (Fig. 4, line e), as well as the physical mixture (Fig. 4, line f), this peak occurred at the slightly lower temperatures of 130 and 128 °C, respectively. Changes in the microenvironment following the inclusion of ATZ could have resulted in weaker association of the water molecules remaining within the cavity, hence reducing the temperature required for their removal. This provides further evidence for the formation of the inclusion complex.

The second peak visible in the thermograms (Fig. 4, line a) is related to the temperature at which thermal degradation of ATZ occurs, with oxidation by atmospheric oxygen and fusion of the compound. For ATZ/CD, as well as the physical mixture (Fig. 4, lines e and f), the peaks were slightly shifted (to 175.6 and 176.5 °C, respectively), relative to the ATZ peak (178 °C), so there was a small reduction in the degradation temperature when ATZ was included within the CD. No peak corresponding to ATZ was observed for CDSI, the ATZ/CDSI complex or the physical mixture of ATZ and CDSI (Fig. 4, lines g, h and i). Formation of the complex might suppress degradation of the molecule, while the large difference between the specific masses of CDSI and ATZ could explain the similarity between these thermograms. In both cases (using CD and CDSI) the thermograms obtained supported the existence of inclusion complexes.

ATZ/SI thermograms, as well as the physical mixture (Fig. 4, lines b and c) showed remaining peaks from ATZ at 176.5 and 178.5 °C respectively. The adsorption of ATZ on pure silica was not observed probably because of the molar ratio used to compare the samples. Although the endothermic peaks decreased, they were not completely suppressed, indicating the main proportion of ATZ.

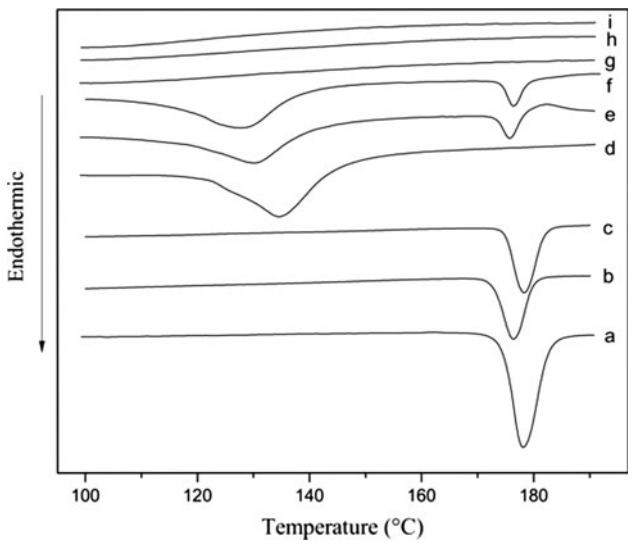

Fig. 4 Differential scanning calorimetry thermograms obtained for *a* ATZ, *b* ATZ/SI, *c* ATZ + SI physical mixture, *d* β-CD, *e* ATZ/CD, *f* ATZ + CD physical mixture, *g* CDSI, *h* ATZ/CDSI, *i* ATZ + CDSI physical mixture

Complexation kinetics

The kinetics of complexation of ATZ in the CD cavity (Fig. 5) was investigated in order to determine the time required for incorporation to occur. Equimolar concentrations (1.391×10^{-5} M) of ATZ and CD were prepared in ultrapure water. The shape of the kinetic curve was in accordance with formation of the ATZ/CD inclusion complex, with increased absorbance being indicative of physico-chemical changes involving the component compounds.

The absorbance showed a rapid increase during the first 40 min, with equilibrium being attained after approximately 2 h. In aqueous solution, the slightly non-polar cavity of the CD is occupied by water molecules. Since interactions between polar and non-polar species are not energetically favorable [23], these water molecules can be substituted by ATZ, which is less polar than water. Inclusion within the CD cavity alters the spectral profile of a substance, since the new microenvironment is different to the original solvation conditions. Analysis of the plot of *ln A* against *t* indicated that the complexation reaction followed first order kinetics, with a rate constant (*k*) of 8.72×10^{-3} min^{-1}. The complexation process was therefore mainly dependent on the concentration of one of the species involved.

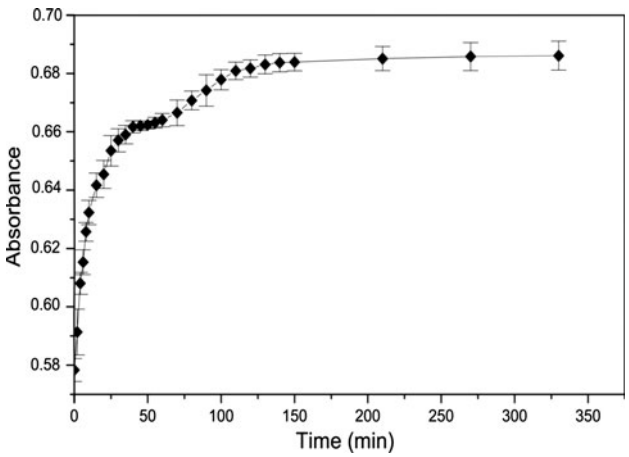

Fig. 5 Kinetics of the complexation of ATZ with β-CD

Solubility kinetics

According to the solubility kinetics (Fig. 6) there was an increase of ATZ in solution during the first two hours of contact with the medium containing CDSI or β-CD, after which a state of equilibrium was reached. Using equimolar mixtures and a temperature of around 25 °C, the solubility of ATZ increased from 0.153 to 0.195 mM in the presence of CDSI and to 0.166 mM in the presence of CD. Solubilization of ATZ was therefore enhanced in both cases, with the largest increase using CDSI.

Solubility isotherms and determination of the association constant

There was an approximately 3.4-fold increase in the concentration of ATZ in water when it was associated with CDSI (Fig. 7, line a). A type A_L isotherm was obtained, with a linear increase in solubility and a stoichiometry of 1:1 for the ATZ/CDSI complex enabling application of Eq. (1), as proposed by Higuchi and Connors [18].

There was a large increase in the solubility of ATZ that was proportional to the increase in the CDSI concentration. For the system containing only β-CD (Fig. 7, line b), the solubility increase was much lower (1.5-fold), which can be explained by the lower association constant of the ATZ/CD complex ($K_a = 28.93$ L mol^{-1}) compared to that of the ATZ/CDSI complex ($K_a = 130.68$ L mol^{-1}).

The association constant of the inclusion complex is an equilibrium constant that provides an indication of the extent of association of the guest molecule (as an inclusion within the CD cavity) relative to the amount remaining free in solution. The numerical value of this parameter is directly proportional to the degree of association of the guest molecule within the interior of the CD [24, 25].

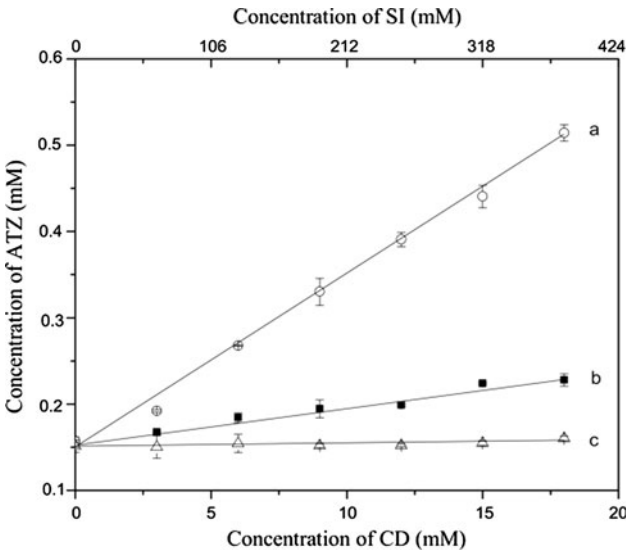

Fig. 7 Solubility isotherms obtained for ATZ in the presence of *a* CDSI, *b* β-CD and *c* silica

Pure silica did not increase the solubility of ATZ. Probably, the anchoring of CD on silica was turning it more available to associate with ATZ. In this case, even increasing the concentration of silica, the solubility of ATZ did not increase (Fig. 7, line c), demonstrating that the adsorption effect was not ruling the increase in solubility in the same way that the inclusion phenomena is.

ATZ release experiments

In the experiments using the dialysis system, the ATZ molecules were able to traverse the pores of the membrane, while the CDs were retained, so that it was possible to determine the influence of complexation on the rate of release of ATZ (Fig. 8).

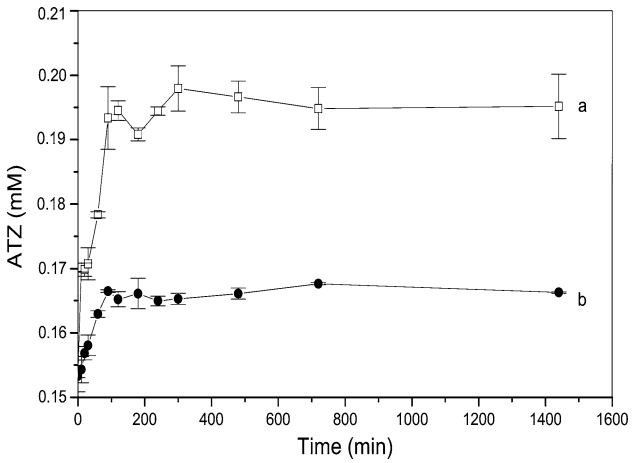

Fig. 6 Solubility kinetics of ATZ using *a* CDSI and *b* β-CD

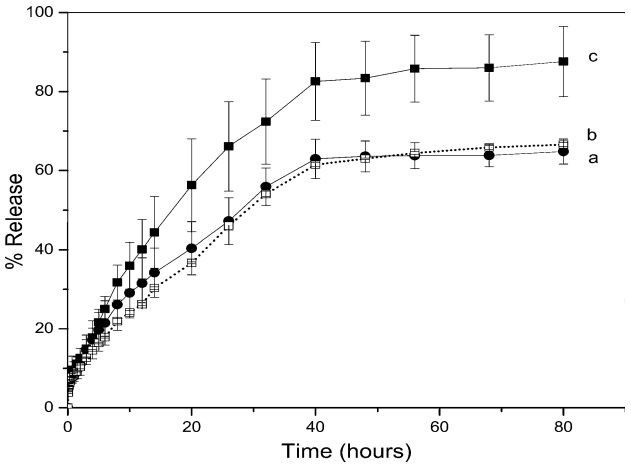

Fig. 8 Release curves obtained for *a* ATZ/CDSI, *b* ATZ/CD and *c* ATZ

For free ATZ (Fig. 8, curve c), around 83% of the chemical was released after 40 h, while following complexation using either CD or CDSI the amount released in the same time period was approximately 62% (Fig. 8, curves a and b). It was therefore clear that association of ATZ with either CDSI or β-CD could alter the release profile of the herbicide, enabling prolongation of its time of action. This suggests that it might be possible to reduce the number of field applications and therefore mitigate problems related to the toxicity of ATZ as well as environmental contamination.

Conclusions

Applications for β-CD and CDSI include improvement of the physical behavior of active agents using processes involving adsorption and controlled release. Complexation of ATZ with CDSI increased the solubility and availability of the herbicide, relative to the free form, with solubility increasing linearly with CDSI addition. An important finding was that the release rate was not influenced by anchoring the CD on silica. Complexation of ATZ using both CDSI and β-CD reduced the release rate, with around 62% being released after 40 h, compared to 83% using free ATZ.

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