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Complexation of chlorpropham with hydroxypropyl-β-cyclodextrin and its application in potato sprout inhibition

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ABSTRACT

The effect of hydroxypropyl-β-cyclodextrin (HPβCD) on the improvement of chlorpropham (CIPC) as a potato sprout inhibitor was investigated. The formation of complex was confirmed by FT-IR spectra, thermoanalysis, ^{1}H NMR and ROESY. The stoichiometry and stability constant were determined by Job's plot and phase solubility studies, respectively. The inclusion complex CIPC·HPβCD has exhibited different properties from CIPC. The obtained inclusion complex was found to significantly improve the water solubility, thermal stability and dissolution rate of CIPC. In addition, the complex displayed a better effect on sprout inhibition.

1. Introduction

Potato sprouting causes increased weight loss, reduced tuber quality and impedes air movement through the potato pile which leads to further acceleration of tuber rot, and make them unacceptable for marketing (Kleinkopf, Oberg, & Olsen, 2003). A major component of managing potato quality in storage is effective sprout inhibition. Chlorpropham (CIPC), isopropyl-3-chlorophenyl carbamate, is a traditional chemical often applied to prevent this problem and increase the storage period. CIPC inhibits sprout development by altering microtubule structure and function resulting in interference with cell division (Campbell, Gleichsner, Alsbury, Horvath, & Suttle, 2010). However, CIPC has a poor water solubility (89 mg/L at 25 °C) (Worthing & Hance, 1991), and it is usually applied as an aerosol in methanolic solution to potatoes in bulk storage through circulation in the air, or by dusting over the tubers, or as dip or spray in wax emulsions (Lu, Donner, Yada, & Liu, 2012). These formulations need a large quantity of organic solvents to improve CIPC's solubility in order to assure its enough bioavailability.

More research had reported the solubility and bioavailability of agrochemicals can be improved by complexation with cyclodextrins (CDs) (Lezcano, Al-Soufi, Novo, Rodríguez-Núñez, & Tato, 2001; Villaverde, Morillo, Pérez-Martínez, Ginés, & Maqueda, 2004; Zhu, Wang, Chen, Yang, & Yang, 2007). CDs are a class of macrocyclic compounds, which are well known to have a hollow truncated cone with a hydrophobic cavity and a hydrophilic wall. They are able to form host–guest complexes with the guest molecules that possess suitable polarity and dimension. After formation of the complexes, the physical, chemical and biological properties of guest molecules can be significantly improved (Szejtli, 1998). Our research previously reported the complexation of CIPC with β-cyclodextrin (βCD), but we found an insoluble microcrystalline complex was formed and the effect of βCD on solubilization of CIPC was limited (Ge et al., 2011).

Therefore, the aim of this work was to establish a possibility of obtaining inclusion complex of CIPC with hydroxypropyl-β-cyclodextrin (HPβCD), which is a hydroxyalkylated βCD derivative that combines relatively high water solubility with low toxicity and satisfactory inclusion ability (Gould & Scott, 2005). The obtained complex supplied a more rational use of CIPC, improving its water solubility and bioavailability. Herein, to explore the host–guest interaction, the complex was characterized by phase solubility diagram, FT-IR spectra, thermoanalysis, ^{1}H NMR and ROESY.

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Additionally, the effect of the complex on sprout inhibition during potato storage was evaluated.

2. Materials and methods

2.1. Materials

HPβCD with molar substitution of 8.64 was purchased from Shandong Xinda Fine Chemical Co., Ltd. CIPC (purity > 99.0%) was obtained from Lianyungang Changtai Chemical Co., Ltd., which was used without further purification. A 30% emulsifiable concentrate (EC) of CIPC was from Engineering and Technology Research Center for Agricultural Product Storage and Processing of Gansu Province. Other chemicals used were of analytical reagent grade. The redistilled water was used throughout.

2.2. Preparation of inclusion complex

HPβCD (65.48 g, 0.04 mol) and CIPC (8.5464 g, 0.04 mol) were completely dissolved in 400 mL of solution of ethanol and water (v/v = 1:20). The solution was stirred at 70 °C for 24 h, then the resulting solution was frozen and lyophilized with a VFD 2000 freeze-drier (Boyikang Experimental Instrument Co., Ltd., China) to obtain the powder. The obtained solid inclusion complex was dried in a vacuum desiccator.

2.3. Preparation of physical mixture

HPβCD (1.6370 g, 1.0 mmol) and CIPC (0.2137 g, 1.0 mmol) were ground into powder, respectively. Particularly, to prevent CIPC from melting, it required to be ground in an ice bath. Then, the two compounds were mixed slightly till the powder was even. Finally, the physical mixture was obtained and dried in vacuum.

2.4. Phase solubility studies

The phase solubility studies were performed according to the method reported by Higuchi and Connors (Higuchi & Connors, 1965). An excess amount of CIPC (10 mg) was added to aqueous solutions (10 mL) containing different concentrations of HPβCD (0, 2, 4, 6, 8, 10, 11 and 12 mM). The flasks were shaken at 25 °C until the equilibrium was reached. Then the suspensions were filtered with syringe through a 0.45 μm hydrophilic membrane filter, and the concentration of CIPC in the filtrate was properly diluted and analyzed at 237 nm using a UV–Vis spectrophotometer (Varian Cary-100). The presence of HPβCD did not interfere with the spectrophotometric assay of CIPC, and the linear regression equation was $A = 12.465\,C\,(\mathrm{mM}) + 0.0167$ ($R = 0.9993$). The apparent stability constant K_c was calculated from the straight line obtained in the phase solubility diagram, where S_0 is the intrinsic solubility of CIPC in redistilled water in the absence of HPβCD:

$$K_c = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

2.5. Characterization of inclusion complex

The FT-IR spectra of HPβCD, CIPC, physical mixture and inclusion complex were recorded by using Thermo Nicolet AVATAR 360 FT-IR spectrophotometer in region 4000–400 cm^{-1}. Potassium bromide pellets were used for all samples.

Thermogravimetry (TG) and differential thermal analysis (DTA) were examined by a PYRIS diamond thermogravimetric/differential thermal analyzer (TG/DTA) 6300 (Perkin Elmer, Inc.), and the samples were sealed in Al_2O_3 crucible. The heating rate was set at 10 °C/min within the temperature range from 25 to 450 °C in nitrogen.

^{1}H NMR spectra were recorded at room temperature on Bruker AVANCE III 400 NMR spectrometer (Germany) using a 5 mm probe and a simple pulse-acquire sequence. Acquisition parameters consisted of spectral width 4000 Hz, acquisition time 5.45 s, number of scans of 8, and relaxation delay of 1 s. Equimolar HPβCD, CIPC and the complex CIPC·HPβCD were respectively dissolved in DMSO-d_6 solution (Aldrich).

Rotating-frame overhauser effect spectroscopy (ROESY) experiments were acquired in the phase sensitive mode with the same spectrometer and Bruker standard parameters (pulse program roesyphpr). For ROESY spectra, the time domain data was zero filled to 1024 points in F2 and 256 points in F1. The ROESY data was acquired with a spin-lock mixing time of 200 ms, and a relaxation delay of 2 s.

A continuous variation method (Job's plot) (Job, 1928) was performed in order to confirm the stoichiometry of the complex. The sum of the concentrations of both components was kept constant ([CIPC] + [HPβCD] = 1 mM) and the molar fraction of each component (r = [CIPC]/([CIPC] + [HPβCD])) ranged between 0 and 1. In order to calculate the stoichiometry, the chemical shift variations ($\Delta\delta$) of the H-3 and H-5 protons of HPβCD were plotted versus the molar fraction (r).

2.6. Dissolution studies

Dissolution studies were carried out using a ZRS-8G dissolution tester (Haiyida, China) at 50 rpm and 37 ± 0.5 °C. Powdered samples, CIPC, its physical mixture and complex, were added to 1000 mL of redistilled water, respectively. Each formulation contained 10 mg CIPC. The samples (5 mL) were withdrawn using a syringe at 5, 10, 15, 20, 25, 30, 35, 40, 50 and 60 min, filtered through 0.45 μm hydrophilic membrane filter, and analyzed by UV spectrophotometer at 237 nm.

2.7. Application in potato sprout inhibition: a preliminary study

Potato cultivar "*Xindaping*" (Dingxi, China) was used in the study. Potatoes were harvested and stored at 15 °C for one month for the curing period prior to treatment. Twenty medium-sized tubers were randomly selected for each treatment. Treatments applied to potato tubers were shown in Table 1, and dip method was used in the experiment (Mondy & Ponnampalam, 1985). The CIPC emulsion dip was used instead of an aerosol spray since previous experiments had shown that emulsion resulted in greater uniformity of application and reproducibility than the aerosol spray (Mondy, Reddy, & Munshi, 1993). After dipping, the tubers were allowed to air dry for 20 min and each treatment was placed in a separate corrugated case. All treatments were stored under 15 °C, and 80–90% relative humidity (RH), with at least 15 cm of distance between them. Tubers were stored for a total of 120 days starting from December 2012 to April 2013. At the end of storage, sprout

Table 1
Applied treatments, methods and effective concentration of CIPC used in the experiment.

Treatments	Methods	Effective concentration of CIPC
No sprout inhibitor	Dipped in water	0
CIPC EC	Dipped in 1.0% a.i. (w/v) water emulsion of CIPC	10 g/L
CIPC·HPβCD	Dipped in 3 g/L complex solution	0.35 g/L

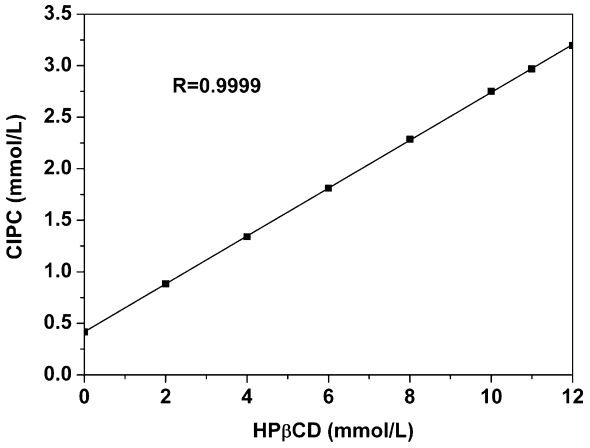

Fig. 1. Phase solubility diagram of CIPC in the presence of HPβCD.

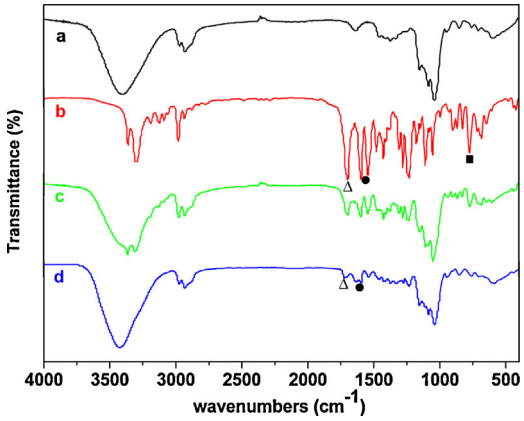

Fig. 2. FT-IR spectra of HPβCD (a), CIPC (b), physical mixture CIPC/HPβCD (c) and inclusion complex CIPC·HPβCD (d).

length (mm) was recorded (Costa, Silva, Galhano, & Moreira Da Silva, 2007; Daniels-Lake, Pruski, & Prange, 2011). The experiments were carried out in triplicate.

3. Results and discussion

3.1. Phase solubility studies

Phase solubility diagram has been extensively used in investigating the solubility of some drugs and agrochemicals in the presence of CDs (Rajabi, Tayyari, Salari, & Tayyari, 2008; Villaverde, Morillo, Pérez-Martínez, Ginés, & Maqueda, 2004). The phase solubility diagram of CIPC in the presence of different HPβCD concentrations (Fig. 1) could be classified as A_L type according to Higuchi and Connors (Higuchi & Connors, 1965). The diagram was a straight line with a slope less than 1, indicated that the formation of a 1:1 inclusion complex between CIPC and HPβCD, and the apparent stability constant K_c calculated according to Eq. (1) was $7.28 \times 10^2\ M^{-1}$. A linear increase up to 7.7-fold in CIPC solubility was observed when increasing HPβCD concentration, and a solubility limit was not obtained in the range of HPβCD concentrations used. However, βCD showed a limited solubilization to CIPC in previously study (Ge et al., 2011). Differences in the affinity between βCD and HPβCD with the same guest indicating that not only the size but also the hydrophobicity of the host are driving forces operating in the complex formation (Pacioni, Sueldo Occello, Lazzarotto, & Veglia, 2008). Due to HPβCD having higher water solubility and a larger hydrophobic cavity, the water solubility of CIPC was significantly improved by complexation with HPβCD.

3.2. FT-IR spectra

The variation of the shape, shift, and intensity of the FT-IR absorption peaks of the guest or host can provide enough information for the occurrence of the inclusion (Szente, 1996). FT-IR spectra of HPβCD (a), CIPC (b), physical mixture CIPC/HPβCD (c), and inclusion complex CIPC·HPβCD (d) were presented in Fig. 2. It can be seen that the spectrum of c was essentially the combination of a and b, indicating that the physical mixture CIPC/HPβCD did not lead to inclusion. However, there were obvious changes in FT-IR spectra after the complex CIPC·HPβCD was formed (Fig. 2d). The band at 1697 cm^{-1} (Δ) corresponding to C=O stretching vibration in secondary amide blue-shifted to 1722 cm^{-1}, the displacement can be interpreted to the changes of the hydrogen bonds interaction (Ginés et al., 1996). In addition, the band at 1597 cm^{-1} and 1545 cm^{-1} (●) attributed to C=C stretching vibration of the benzene ring blue-shifted to 1635 cm^{-1} and 1598 cm^{-1}, respectively, and their intensity decreased in the complex. At the same time, the bands at 901, 773 and 683 cm^{-1} (■) corresponding to C—H bending vibrations for meta-substituent of benzene ring disappeared. Therefore, FT-IR spectra confirmed the inclusion complex CIPC·HPβCD was formed.

3.3. Thermoanalysis

Some evidence of the formation of inclusion complex was obtained from thermal behavior studies. When guest molecules were embedded in HPβCD cavities, their melting, boiling or sublimation point generally could shift to a different temperature or disappear within the temperature range where HPβCD was decomposed (Su, Rao, Cai, & Yang, 2010). The TG-DTA thermograms obtained for HPβCD(a), CIPC(b), physical mixture CIPC/HPβCD(c), and the complex CIPC·HPβCD(d) were presented in Fig. 3. HPβCD lost weight in two steps at 50–100 °C and 330–380 °C (Fig. 3a). According to DTA curve, the former was associated with the evaporation of water that had been adsorbed by HPβCD; the latter was caused by the decomposition of HPβCD. The DTA curve of CIPC (Fig. 3b) showed the exothermal peak at 50 °C, assigned to its melting point. Besides, CIPC had a single weight loss step at 150–220 °C from TG curve, associated with the decomposition of CIPC. For physical mixture, Fig. 3c, represented the TG-DTA curve of CIPC/HPβCD was the superposition of the curves of HPβCD and CIPC, indicating the occurrence of non-inclusion interactions. The TG-DTA curves of inclusion complex (Fig. 3d) were quite different from the curves of free compounds and the physical mixture, the peak corresponding to the melting point (50 °C) and decomposition (222 °C) of CIPC disappeared. In particular, the weight loss of CIPC in the complex occurred at 240–280 °C, which indicated that the formation of CIPC·HPβCD complex retarded the weight loss of CIPC during heating. These findings were consistent with the literature (Garnero, Aiassa, & Longhi, 2012; Su, Rao, Cai, & Yang, 2010), in which the thermal stability of guest molecule was improved when it was complexed with HPβCD.

3.4. NMR spectra

^{1}H NMR spectra are one of the most direct evidence for the formation of the inclusion complex (Yuan, Jin, & Xu, 2012). The interactions between host and guest molecules are noncovalent bonds such as Van der Waals forces, hydrophobic interactions and hydrogen bonds (Jiang et al., 2007). If the guest molecule is incorporated into the HPβCD cavity, their chemical shifts will be changed. Especially, the screening constants of the HPβCD protons inside the cavity (H-3 and H-5) should be more sensitive to

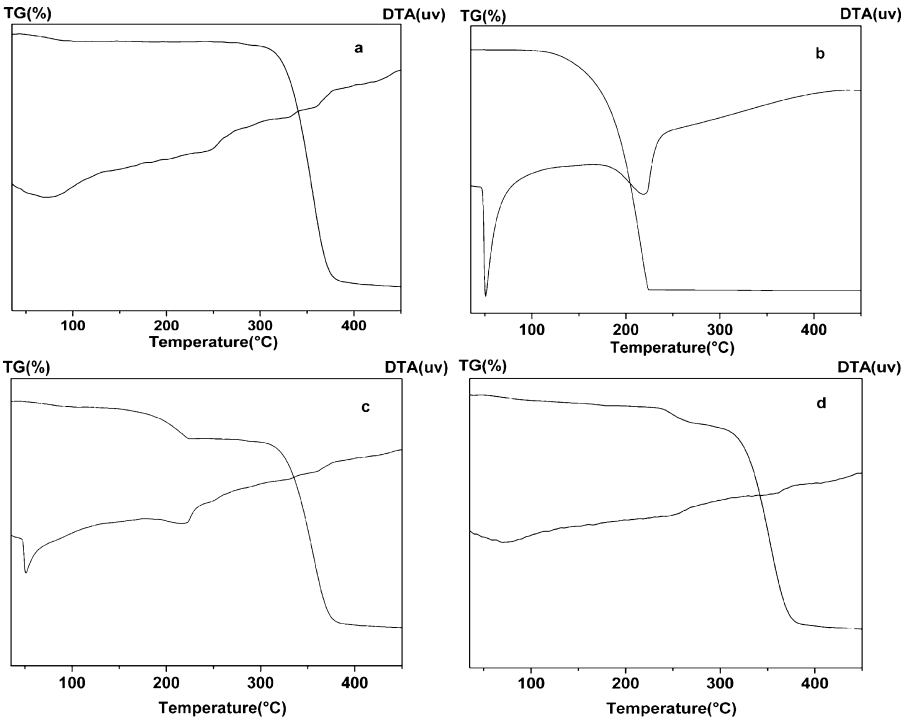

Fig. 3. TG-DTA thermograms of HPβCD (a), CIPC (b), physical mixture CIPC/HPβCD (c) and inclusion complex CIPC·HPβCD (d).

the changed environment (Polyakov, Leshina, Konovalova, Hand, & Kispert, 2004). Fig. 4A shows ^{1}H NMR spectrum of HPβCD (a), CIPC (b), and inclusion complex CIPC·HPβCD (c) in DMSO-d_6. All hydrogen protons of CIPC and H-3, H-5 of HPβCD were assigned. After the complex was formed, the H-3 and H-5 protons of HPβCD presented upfield shift (blue dashed) owning to the anisotropic magnetic effect induced by the presence of the aromatic group of the guest molecule (Veiga, Fernandes, Carvalho, & Geraldes, 2001).

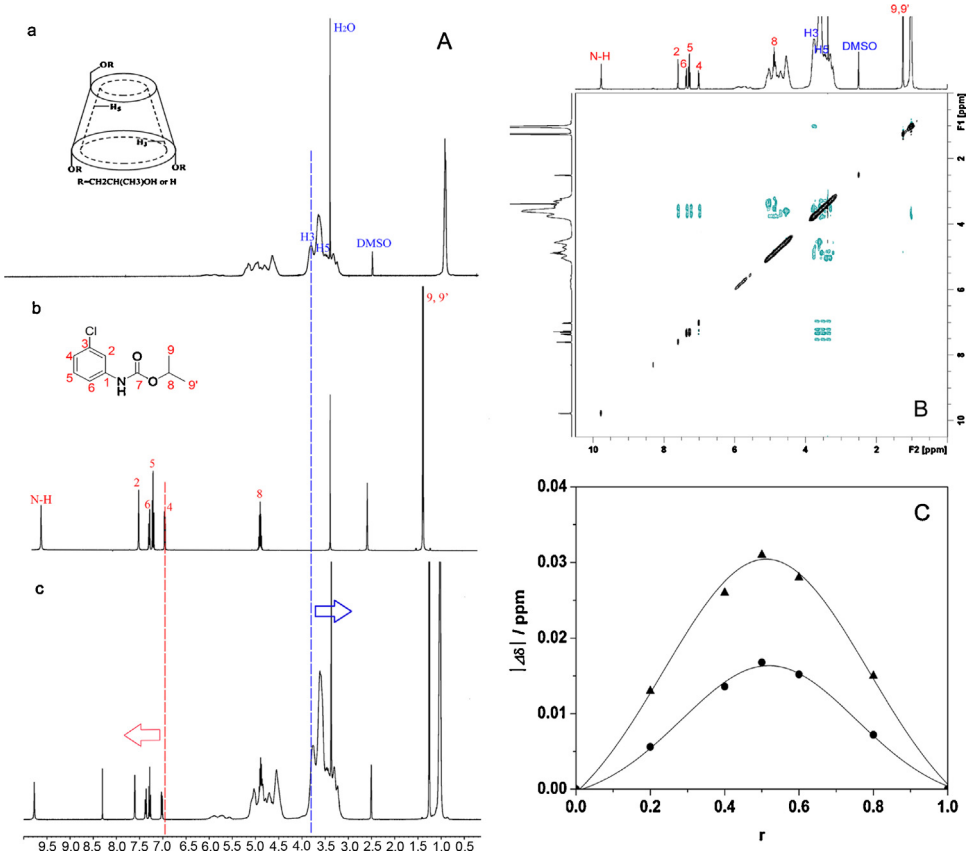

Fig. 4. (A) ^{1}H NMR spectra of HPβCD (a), CIPC (b), physical mixture CIPC/HPβCD (c) and inclusion complex CIPC·HPβCD (d) in DMSO-d_6; (B) portion of the ^{1}H–^{1}H ROESY spectrum for inclusion complex CIPC·HPβCD; (C) Job's plot for the determination of the stoichiometry of the complex from NMR measurements: H-3 (▲) and H-5 (●).

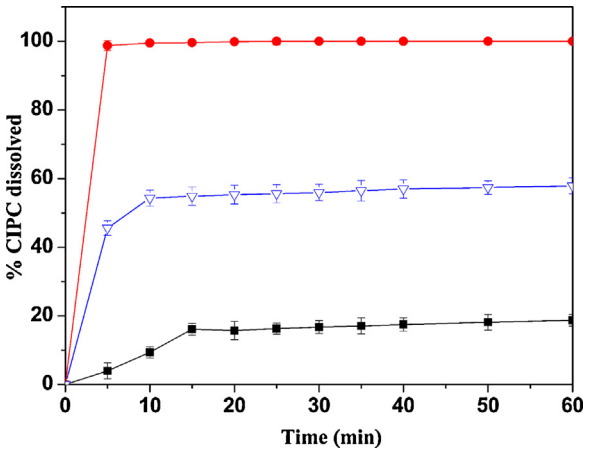

Fig. 5. Dissolution curves in water of CIPC (■), its physical mixture CIPC/HPβCD (▽) and inclusion complex CIPC·HPβCD (●).

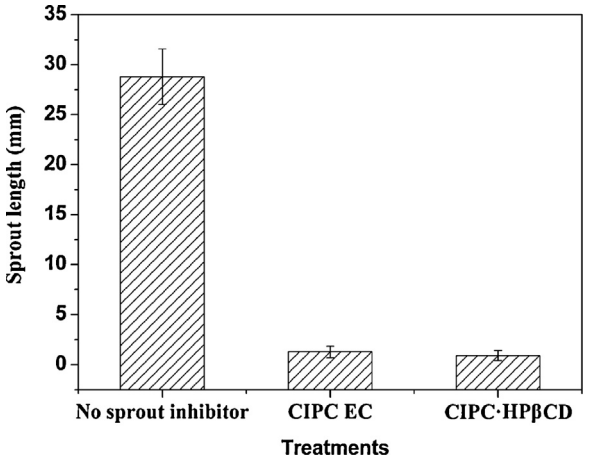

Fig. 6. Sprout length of tubers stored at 15 °C after 120 days.

On the contrary, only signals for chlorophenyl protons of CIPC showed downfield shift changes (red dashed) upon complexation with HPβCD because of Van der Waals deshielding. It was suggested that the chlorophenyl moiety of CIPC was included into the HPβCD cavity.

Afterwards, the mode of the inclusion complex was further conformed by 2D NMR spectroscopy since cross-peaks in ROESY spectra are expected for protons that are closer than 4 Å in space (Schneider, Hacket, Rüdiger, & Ikeda, 1998). As can be shown in Fig. 4B, the protons H-2 (s, δ 7.603 ppm), H-4 (d, δ 7.008–7.030 ppm), H-5 (t, δ 7.261–7.301 ppm) and H-6 (d, δ 7.359–7.379 ppm) of CIPC had cross peaks to the H-3 and H-5 protons of HPβCD, indicating the deep insertion of the CIPC's chlorophenyl moiety into the host cavity. No cross peaks between the isopropyl protons of CIPC and the protons within the cavity of HPβCD were observed.

The Job's method was performed in order to confirm the results that the former studies revealed about the stoichiometry of the complex. The plot observed in Fig. 4C showed the maximum at a molar fraction of about 0.5, indicating that the stoichiometry of the complex CIPC·HPβCD was 1:1 in agreement with phase solubility studies.

3.5. Solubility

The supersaturated solutions of CIPC and the complex were prepared, respectively. Then the suspensions were sufficiently shaken and filtered with syringe through a 0.45 μm membrane filter. The concentrations of CIPC in the filtrates were properly diluted and analyzed at 237 nm. The experiments were repeated five times. According to the standard work curve, the solubility of CIPC in complex was 371.85 mg/L (R.S.D. = 2.28%). It was showed that the solubility of CIPC was improved more than four times after complexation with HPβCD, which obtained a better solubility than complexation with βCD (Ge et al., 2011).

3.6. Dissolution studies

Fig. 5 shows the dissolution profiles of free CIPC, physical mixture CIPC/HPβCD and complex CIPC·HPβCD. The dissolution pattern of CIPC was found to be very slow, in accordance with its poorly water-soluble property. As expected, the complex exhibited markedly faster dissolution than that of pure drug and physical mixture, nearly 100% of the loaded drug dissolved after 5 min, indicating the remarkable effect of inclusion technique using HPβCD in promoting dissolution rates. Owing to the hydrophilicity of the exterior surface of HPβCD, CIPC molecules insertion into the HPβCD cavity improved their wettability (Vandelli et al., 1995). In addition, the high energetic amorphous state of the freeze-dried products might also enhanced dissolution of the complex.

3.7. Application in potato sprout inhibition: a preliminary study

A recent Environmental Protection Agency mandate, from the requirements of the Food Quality Protection Act (FQPA) of 1996, resulted in a reduction in allowable CIPC residue on fresh potatoes in the United States from 50 ppm to 30 ppm (Sharma, 2012). Therefore, the purpose to minimize the dose of CIPC while assure enough efficacy for sprout inhibition was required. In the experiment, three treatments were designed to apply for potato tubers. According to solubility results above, solution concentration of 3 g/L CIPC·HPβCD within its solubility was chosen. The effective concentration of CIPC in the complex soak was only 0.35 g/L, which was far less than commercial available 1.0% CIPC EC (10 g/L). The potato tubers began to sprout after about 90 days both in CIPC EC and CIPC·HPβCD treatments, while 55 days in no sprout inhibitor treatment. It was indicated that the two CIPC formations can control

Fig. 7. Potatoes without sprout inhibitor treated (left), potatoes treated with CIPC EC (middle) and the complex CIPC·HPβCD (right) after 120 days storage at 15 °C.

tubers sprouting in the same time. At the end of the storage (after 120 days), as presented in Fig. 6, the shortest sprout length was found in CIPC·HPβCD (0.9 mm) treatment among the whole treatments. No sprout inhibitor and CIPC EC treatments had 28.8 mm and 1.3 mm sprout length, respectively. The complex treatment had the best effect on potato sprout inhibition than others (Fig. 7), indicating that the formation of the complex significantly improved the bioavailability of CIPC due to the improvement of the water solubility.

4. Conclusions

In this work, the complex CIPC·HPβCD with host–guest ratio 1:1 has been prepared. Phase solubility studies, FT-IR, thermoanalysis and NMR spectra were applied to characterize the complex formation. The stability constant of the inclusion complex was found to be $7.28 \times 10^2\ M^{-1}$ according to the phase solubility diagram, and the stoichiometry was conformed by the Job's plot. One-dimensional ^1H NMR and ROESY experiments indicated that the mode of the complex in which the chlorophenyl moiety of CIPC encapsulated within the HPβCD cavity. By complexation with HPβCD, the solubility and dissolution of CIPC were significantly improved.

In addition, CIPC presented the great increase of bioavailability after formation of the complex, which providing an effective approach for a more rational application of CIPC, diminishing the usage of organic solvents and the dose of CIPC applied on potato tubers. Therefore, the complex CIPC·HPβCD can be considered as a potential new sprout inhibitor. Further studies should be done in order to clarify the economic advantages of the use of the complex CIPC·HPβCD as potato sprout suppressant.

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