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ORIGINAL ARTICLE

Release characteristics of the non-toxic insect repellant 2-undecanone from its crystalline inclusion compound with α-cyclodextrin

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Abstract 2-Undecanone (methyl nonyl ketone), a natural non-toxic insect repellant compound, was recently isolated from the trichomes of wild tomatoes, and is currently being introduced as a replacement for insect repellants containing *N*,*N*-diethyl-meta-toluamide or DEET, which are permitted for use on children older than 2 months. In an effort to improve the delivery of the somewhat volatile 2-undecanone, we have successfully formed the crystalline inclusion compound (IC) between 2-undecanone and α-cyclodextrin (α-CD), using a coprecipitation method. Employing WAXD, DSC, FT-IR, and NMR observations, we have confirmed that 2-undecanone is included as a guest inside the host α-CD cavities, and forms a channel-type crystalline IC. The release characteristics of 2-undecanone insect repellant from its α-CD-IC were studied using TGA either at a heating rate of 20 °C/min in nitrogen, and air atmospheres or at constant temperatures of 25, and 40 °C over a period of 24 h. The release/loss of 2-undecanone insect repellant from its α-CD-IC was ~60% after 24 h at 40 °C. By comparison, ~97% of pure 2-undecanone was volatilized, and lost over 24 h at 40 °C. In addition, insecticidal activity of 2-undecaonone from its α-CD complex against German cockroaches was evaluated. The results show an excellent repellency that 100% of the cockroaches were repelled for the first 2 days after application. These results suggest that the gradual, long-term delivery of the insect repellant 2-undecanone can be significantly improved through employment of its crystalline α-CD-IC.

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Keywords Cyclodextrins · Inclusion complexes · Insect repellant · 2-undecanone · Controlled release characterisitcs

Introduction

N,*N*-diethyl-meta-toluamide (DEET) is the active ingredient most commonly used in insect repellant products. It is used to repel biting pests, such as ticks, mosquitoes, and cockroaches, which carry many diseases. Almost one-third of Americans use DEET products every year, from among the ~140 that are currently registered with the U.S. Environmental Protection Agency (EPA). Although the safety of DEET has been questioned, EPA concluded that insect repellants containing DEET do not present a health concern, if people follow label directions when using DEET-based insect repellant products. However, the EPA recommended improved label warnings, and restrictions for DEET use, especially with children, although there is no current restriction on the percentage of DEET in the product for use on children over 2 months old [1].

In 2002, scientists at North Carolina State University discovered a natural insect repellant compound, methyl nonyl ketone, or 2-undecanone, isolated from the trichomes of wild tomatoes, which was licensed by HOMS, LLC. Their formulations contain either 8% or 30% 2-undecanone, and are commercialized under the trade names BioUD8® and BioUD30®, respectively. In 2007, EPA approved BioUDs® as a replacement for DEET to be used in child-safe insect repellants. Also, the repellent activity of the products against the American dog tick was evaluated [2–5].

One potential disadvantage of 2-undecanone as an insect repellant is its relatively high volatility. Hence, BioUD® products have been incorporated into a proprietary

emulsion in order to reduce the evaporation rate of 2-undecanone, and prolong its effectiveness as an insect repellant. Various technologies have been developed over the years for protection, isolation, or controlled release of ingredients in order to achieve better performance, and greater value. It has been reported that complexation of deliverable guests with cyclodextrins (CDs) can provide various advantages for preventing losses due to volatilization, oxidation, thermal degradation, and storage. For example, the crystalline CD inclusion compound (IC) containing menthol guests has a much more prolonged shelf life, compared with pure menthol, which readily sublimes at room temperature. Formation of a similar CD-IC with guest vitamin A palmitate increased its half-life against photodegradation, while the pure vitamin degrades rapidly when exposed to light. CD encapsulation of volatile pesticides resulted in improvements in their fluidity, wettability, and thermal stability [6, 7]. There are also patents, and papers describing CD-ICs formed with guests including insect repellants, and those intended for sustained-release [8–23]. However, no studies concerning the formation of and controlled release of the non-toxic insect repellant 2-undecanone from inclusion complexes have been reported.

Cyclodextrins are produced by the glucosyltransferase enzymatic degradation of amylase starch, and are composed of glucose units α-linked through 1,4-glycosidic bonds. The most commonly produced, and utilized varieties are α-, β-, and γ-CD, containing six, seven, and eight glucose units, respectively. They have a truncated conical shape, and a hollow interior or cavity, with all the glucose units in substantially undistorted chair conformations, resulting in a unique arrangement of their –OH functional groups. The secondary hydroxyl groups are located on one rim of the torus, while the primary hydroxyl groups are located on the opposite rim (Fig. 1).

CDs can form inclusion compounds with various guest molecules. Their versatile capability to bind so many different guest materials is due to the nature of their internal cavities. There are two different forms of crystalline inclusion complexes (ICs), channel, and cage-type structures. Channel structures develop when CDs stack on top of one another to yield endless channels, in which guest molecules are included. Cage structures are a result of a displaced arrangement of CDs, in which entire or small parts of larger guest molecules are located in the cavities represented by the annular CD apertures (Fig. 2) [24–30].

In this study, the natural, non-toxic insect repellant, 2-undecanone, was successfully included in α-CD and their crystalline complex (IC) was confirmed using Fourier Transform Infrared (FT-IR), and Nuclear Magnetic Resonance (NMR) spectroscopies, Differential Scanning Calorimetry (DSC), and Wide Angle X-ray Diffraction (WAXD). Controlled release characteristics of guest 2-undecanone insect repellant from its α-CD-IC crystals was examined using Thermogravimetric analysis (TGA). In addition, insecticidal activity of 2-undecanone from its α-CD inclusion complex was determined using German cockroaches.

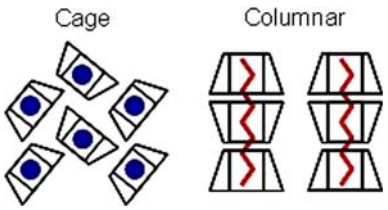

Fig. 2 Crystalline CD inclusion compounds with cage and channel structures, containing included small and long guest molecules, respectively

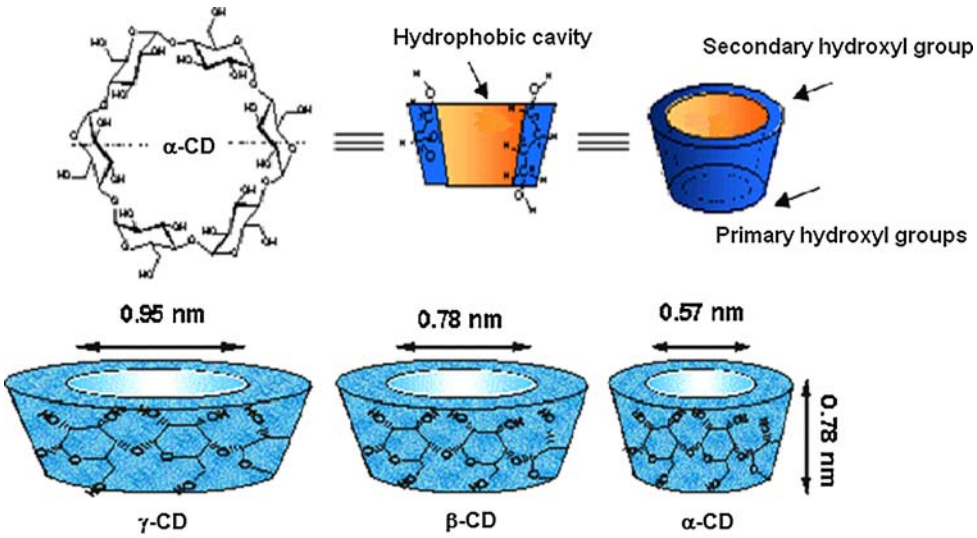

Fig. 1 Cyclodextrin structures and dimensions

Experimental

Materials

2-undecanone, and α-cyclodextrin were obtained from the Department of Entomology at North Carolina State University, and Cerestar Company, respectively, and were used as supplied.

Preparation of 2-undecanone-α-CD-IC

2-undecanone-α-CD-IC was prepared by slowly adding 0.26 g of 2-undecanone dissolved in acetone (5 mL) to 13.8 mL of an aqueous solution saturated with α-CD (2.0 g of α-CD) held at 60 °C. After 2 h of stirring, the covered flask was removed from the hot plate. Then, the solution was left unperturbed overnight, a white precipitate was formed. It collected by filtration, and the crystals were washed with distilled water, and air-dried. The amount of 2-undecanone included in the α-CD complexes was quantified with the following method: a total of 100 mg complex was dissolved in 50 ml water–ethanol (1:1 mixture) and the absorbance was measured at 268 nm by a UV-VIS spectrophotometer (Cary 3E, Varian, Inc., USA).

Characterization

X-ray diffraction

X-ray diffraction data were collected from the prepared 2-undecanone-α-CD-IC powder under the following conditions: Siemens type-F X-ray diffractometer, Ni-filtered Cu K_α radiation with a wavelength of 1.54 Å, voltage at 30 kV, current at 20 mA, and scanning speed of $2\theta = 5°$/min, over the range of $2\theta = 5$–$30°$.

Fourier Transform Infrared spectroscopy

A Nicolet 510P FTIR spectrometer was used for observing the infrared spectra of samples between 500 and 4000 cm^{-1} with a resolution of 2 cm^{-1}. α-CD and 2-undecanone-α-CD-IC samples were mixed with KBr, and pressed into transparent disks. 2-undecanone was observed by Attenuated Total Reflectance (ATR).

Nuclear Magnetic Resonance spectroscopy (NMR)

^{1}H-NMR solution spectra of 2-undecanone-α-CD-IC, α-CD, and 2-undecanone were recorded on a Bruker Avance 500 MHz spectrometer in 50% D_2O:50% acetone-d_6. One-dimensional ^{1}H data sets contained 16 K data points, and scans sufficient to obtain good S/N were collected.

Differential scanning calorimetry (DSC)

The experiments were performed on 3–10 mg of 2-undecanone-α-CD-IC and 2-undecanone, with a Perkin-Elmer DSC 7, under nitrogen purge gas, and at a heating rate of 20 °C/min.

Thermogravimetric analysis of 2-undecanone release from its α-CD-IC

The release of 2-undecanone insect repellant from its α-CD-IC was measured on a Perkin-Elmer Pyris 1 thermogravimetric analyzer. Samples (5–10 mg) were placed in an open platinum pan that was hung in the furnace, and the samples were either heated at a rate of 20 °C/min or maintained at a constant temperature over a 24 h period. The weight percentage of remaining material in the pan at various temperatures or at various times at 25 and 40 °C were recorded in either nitrogen or air atmospheres. The amount of release of 2-undecanone from its α-CD complexes was determined by following two steps: firstly, TGA analysis at 40 °C for 24 h was done. Then, the complex (5 mg) was dissolved in 10 mL water–ethanol (1:1 mixture) and the absorbance was measured at 268 nm using UV-VIS spectrophotometer (Cary 3E, Varian, Inc., USA).

Insecticidal activity of 2-undecanone from its α-CD complex against cockroaches

German cockroaches (Blatella Germanica nymphs) were obtained from the Department of Entomology at North Carolina State University. All tests were conducted at room temperature (21 ± 1 °C), and relative humidity ($65 \pm 3\%$). The testing area was constructed with a plastic petri dish (diameter = 60 mm, height = 15 mm) covered with the lid of the dish. The side and lid of the dish were coated with vaseline in order to prevent cockroaches from climbing off the side, and lid of the petri dish, thereby limiting the cockroaches to either side, and the top of the lid of the petri dish. However, cockroaches had enough room to freely move about the arena.

α-CD (2 g) was placed on one half of the petri dish surface. 2-undecanone-α-CD-IC (2 g) was placed on the other half of the petri dish surface. Six cockroaches were transferred into the center of the arena, then the lid was placed on the plastic petri dish. The distribution of cockroaches was checked at 5, 10, 15, 30, and 90 min after the start of the assay. Cockroaches that were in contact with both the α-CD and 2-undecanone-α-CD-IC at the center margin where the two samples meet were not counted in determining the percent repellency. The experiment was conducted in the dark except during monitoring of cockroaches distribution. The sample was stored at room

temperature, and the same sample was re-assayed over the course of 6 days. After three experimental replications, the mean percent repellency was calculated by subtracting the number of cockroaches on the side of α-CD from number of cockroaches on the side of 2-undecanone-α-CD-IC divided by total number of cockroaches.

Results and discussion

Characterization

The X-ray diffractogram of the inclusion compound sample was primarily used to verify the successful inclusion of the 2-undecanone guest. It is well known that the diffraction peak at $2\theta = 20°$ in the WAXD of α-CD-ICs is characteristic for the channel structure produced by inclusion of long guest molecules, such as 2-undecanone [31], and is absent in the diffractogram of pure cage structure α-CD. Hence, the strong peak observed for 2-undecanone-α-CD-IC at about 20° (2θ) in Fig. 3 confirms the channel crystalline structure of 2-undecanone-α-CD-IC, suggesting the inclusion of 2-undecanone.

When 2-undecanone is complexed, it is surrounded by the cyclodextrin channel walls preventing interactions with other 2-undecanone molecules. Therefore, 2-undecanone in the complex is unable to crystallize. The DSC technique was used to determine whether the inclusion compounds obtained contained additional unincluded free 2-undecanone guest molecules. According to Ref. [32], pure 2-undecanone melts at about 15 °C, which is confirmed by its melting peak seen in Fig. 4. The absence of the 2-undecanone melting peak in the heating scan of 2-undecanone-α-CD-IC indicates that it contains no free uncomplexed 2-undecanone.

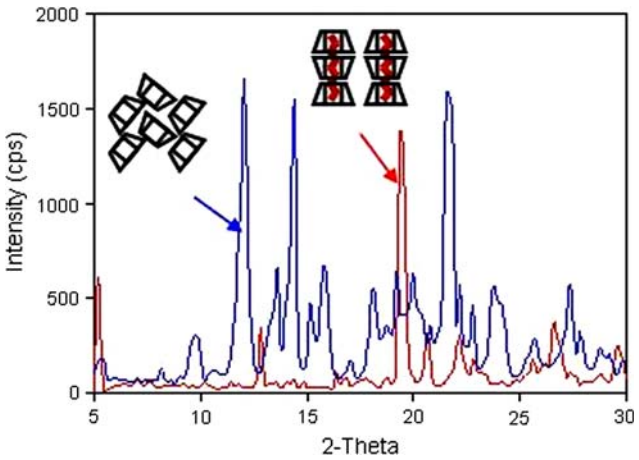

Fig. 3 Wide angle X-ray diffraction of 2-undecanone-α-CD-IC (red) and pure cage α-CD (blue)

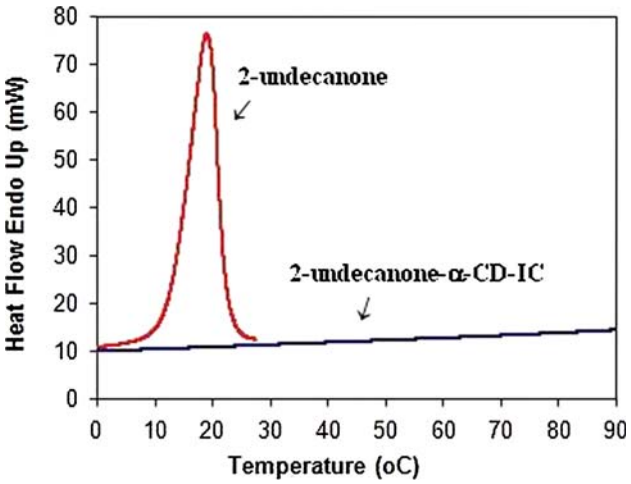

Fig. 4 DSC scans of 2-undecanone and 2-undecanone-α-CD-IC

Figure 5 shows the FTIR spectra of α-CD, 2-undecanone, and 2-undecanone-α-CD-IC. The α-CD spectrum shows bands at 3,390 and 2,926 cm^{-1}, due to the symmetric and anti-symmetric O–H stretching, and C–H stretching modes, respectively. Also, several peaks in the 1,500–1,200 cm^{-1} region are assigned to CH, CH_2, and O–H bending modes. The infrared spectra of α-CD and 2-undecanone-α-CD-IC are very similar. However, careful observation reveals bands appearing in the 2,852 and 1,712 cm^{-1} regions of the 2-undecanone-α-CD-IC spectrum, which are recognized as belonging to 2-undecanone. Hence, the observation of these new bands confirms that 2-undecanone is indeed included inside the channels provided by α-CD in the IC.

NMR provides an additional means to verify complex formation [24]. ^{1}H-NMR spectra of α-CD, 2-undecanone, and 2-undecanone-α-CD-IC dissolved in 50:50 D_2O:acetone-d_6 were recorded, and are presented in Fig. 6. The proton spectra of 2-undecanone and α-CD did not reveal any impurities which could interfere with the accuracy of the NMR spectral analyses. Proton resonances in the 2-undecanone-α-CD-IC, α-CD, and 2-undecanone at about 4.5 and 2.1 ppm were identified due to D_2O and acetone-d_6, respectively. The peaks corresponding to the H1, H3, and H11 of 2-undecanone were identified at about 2.4, 2.1, and 0.7 ppm, respectively (although H3 is overlapped with the acetone-d_6 peak). The peaks at about 1.4 ppm are contributed to H5 and H6 of the 2-undecanone, and the peaks at about 1.1 ppm are contributed to H4, H7, H8, H9, H10 of the 2-undecanone. The peaks corresponding to the H1, H3, H6, H5, H2, and H4 of the α-CD were identified at about 4.9, 3.8, 3.75, 3.68, 3.52, and 3.48 ppm, respectively. ^{1}H-NMR resonances from both α-CD, and 2-undecanone appear in the spectrum for dissolved 2-undecanone-α-CD-IC, confirming the formation of the crystalline 2-undecanone-α-CD-IC. In addition, the stoichiometry of the

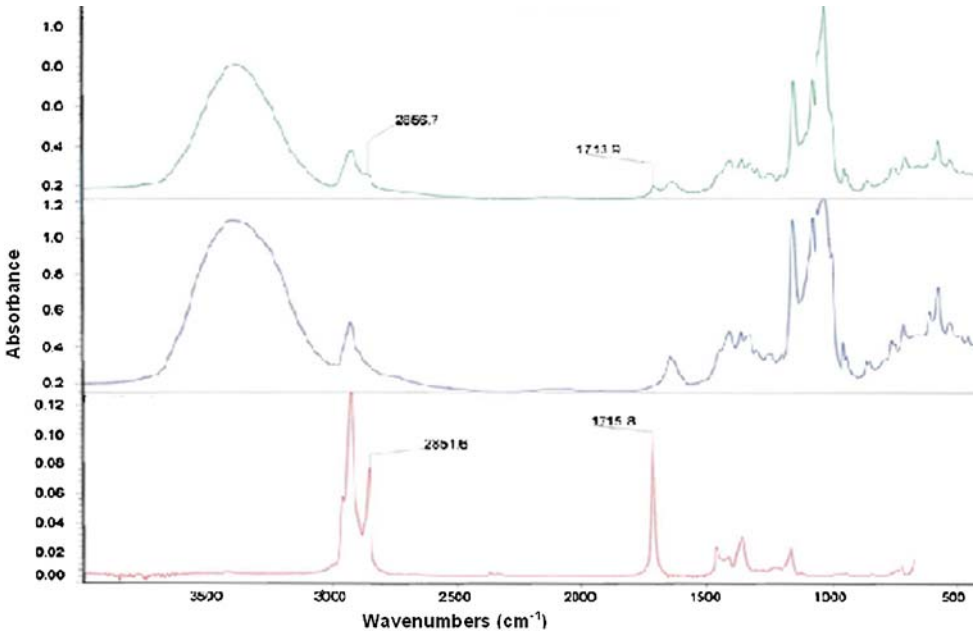

Fig 5 Fourier transform Infrared spectra of 2-undecanone-α-CD-IC (top), α-CD (middle), and 2-undecanone (bottom)

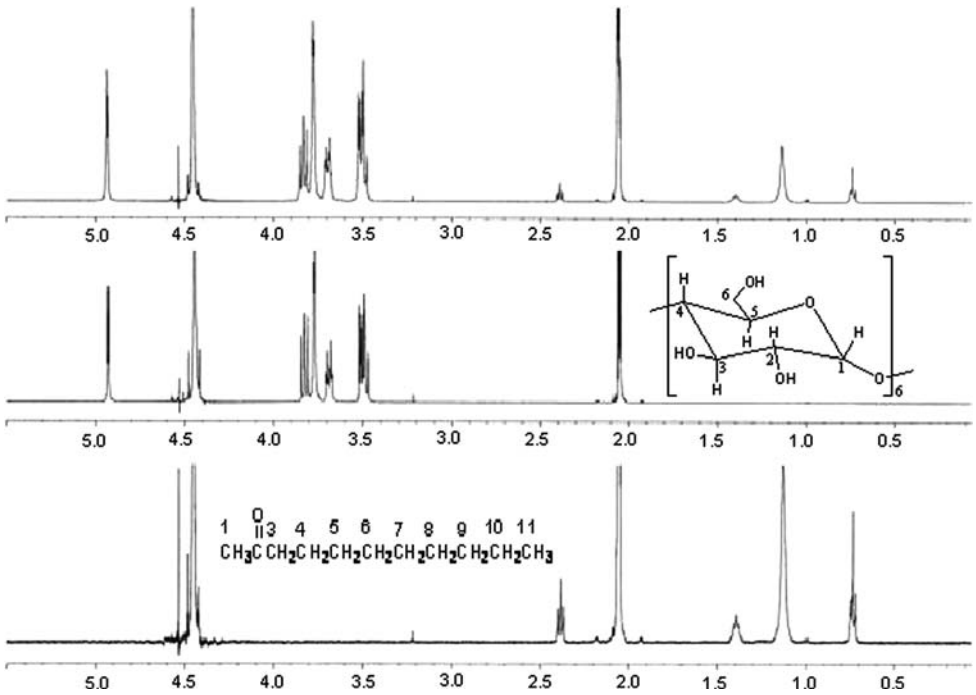

Fig. 6 ^{1}H-NMR spectra of 2-undecanone-α-CD-IC (top), α-CD (middle), and 2-undecanoner (bottom) in 50:50 D_2O acetone-d_6

inclusion complex is obtained directly from the ^{1}H-NMR spectrum of 2-undecanone-α-CD-IC by integrating, and comparing the areas of resonance peaks contributed by 2-undecanone, and α-CD. It was found that α-CD forms a 2:1 inclusion complex with 2-undecanone. In addition, the amount of 2-undecanone included in the α-CD complexes was determined using UV spectrophotometer, and hence it is confirmed that α-CD forms a 2:1 inclusion complex with 2-undecanone.

Evaluation of 2-undecanone insect repellant release from its α-CD complex

The thermal stability, and decomposition behavior of the complex, and a-CD were observed using TGA, as shown in Fig. 7. The onset of thermal decomposition of the complex is ~360 °C, which is slightly higher than that of pure α-CD. Moisture-loss from pure cage α-CD was different compared to the channel structure complex. The TGA scan

of pure α-CD shows two moisture-loss stages at about 75 and 120 °C. This may be due to the fact that two water molecules are located inside the α-CD cavity, and the other four are outside or between α-CDs [33]. Pre-existent water inside the α-CD cavity is replaced by 2-undecanone molecules during formation of its α-CD-IC, hence, when 2-undecanone is released from its α-CD-IC, water from outside the cavities replaces 2-undecanone, and goes inside of the α-CD cavities. Therefore, the water released from the 2-undecanone-α-CD-IC must come from outside the cavities.

The release of 2-undecanone insect repellant from the inclusion complex was determined by measuring percent weight loss at 25 and 40 °C over a 24 h period, as illustrated in Fig. 8. In general, release of the insect repellant from the complex exhibits similar trends in air and nitrogen atmospheres, but release was slightly faster at 40 than at 25 °C. The 24 h release of insect repellant from the complex was about 60% at 40 °C. Further, the remaining amount of 2-undecanone from the complexes was determined using UV spectrophotometer after TGA analysis at 40 °C over a 24 h period which confirmed that 60% of the 2-undecanone from the complex was released. On the other hand, the disappearance/volatilization of pure 2-undecanone accelerated with time, and steadily increased up to 24 h. At 40 °C 97% 2-undecanone was lost after 24 h, respectively, indicating that 2-undecanone was almost completely volatilized after 24 h. The volatilization of pure 2-undecanone was ∼20 times faster than that from the 2-undecanone-α-CD-IC. Obviously, complexation with α-CD to form a crystalline IC can significantly reduce the loss of 2-undecanone by volatilization.

Evaluation of insecticidal activity of 2-undecaonone from its α-CD complex

Figure 9 shows mean percent repellency of 2-undecanone from its α-CD complex against cockroaches. The 2-undecanone-α-CD-IC significantly repelled the cockroaches as shown in Fig. 9. Until 1 day after application, the sample showed an excellent repellency that 100% of the cockroaches were repelled at all time intervals. Two days after application, 67% of the cockroaches were repelled during the 5 min time interval with the exception of the 10 min time point, however, 100% of the cockroaches were repelled in the 15 and 30 min time interval. Three and four days after application, 50% of the cockroaches were repelled during the 5 min time interval, and 83% of the cockroaches were repelled in the 15 and 30 min time intervals. Five days after application, 33% of the cockroaches were repelled at 5, 10, 15, and 30 time slot, and 66% of the cockroaches were repelled at 60 and 90 min time slot. The results from the sixth monitoring day were highly variable with cockroaches repellencies of 33%

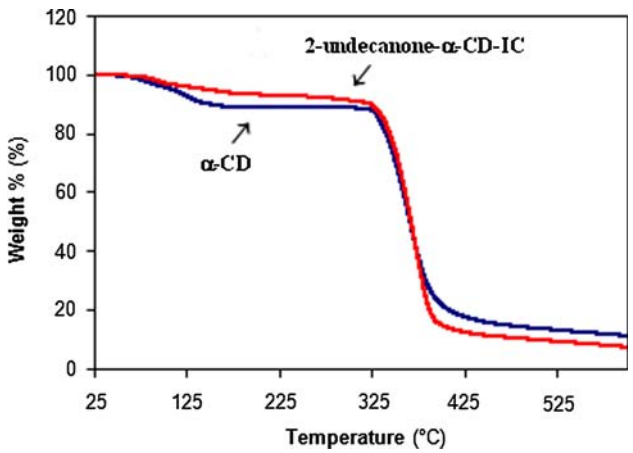

Fig. 7 TGA scans of α-CD (blue) and 2-undecanone-α-CD-IC (red)

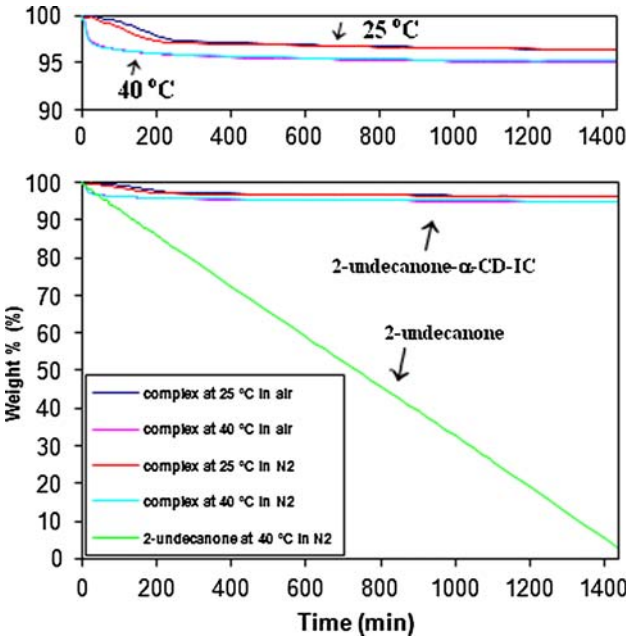

Fig. 8 Time-dependent, constant temperature TGA scans of pure and α-CD-complexed 2-undecanone

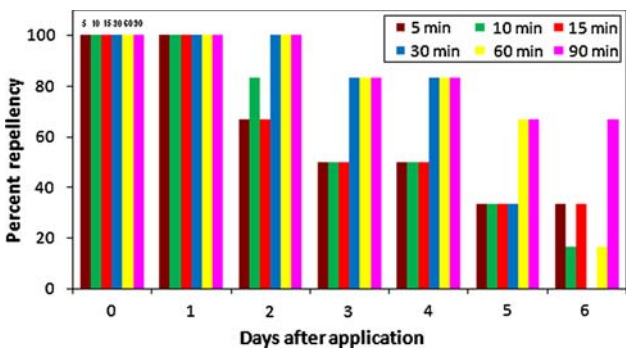

Fig. 9 Insecticidal activity of 2-undeconone from its α-CD complex against cockroaches

(5 min), 17% (10 min), 33% (15 min), 0% (30 min), 17% (60 min), and 66% (90 min).

Conclusions

Formation, and characterization of 2-undecanone-α-CD-IC verified that 2-undecanone guests are included inside the channels provided by the orderly stacking of host α-CD molecules, and form a channel-type crystalline inclusion compound. The controlled release of 2-undecanone insect repellant from the complex was monitored by TGA observations over 24 h at two different temperatures, and also as a function of temperature at a heating rate of 20 °C/min. Increasing temperature accelerated the release of 2-undecanone. The 24 h losses of pure 2-undecanone, and 2-undecanone guests from the complex with α-CD were ~97% and 60%, respectively, at 40 °C. Thus, complexation with α-CD can substantially prevent the loss of 2-undecanone. Because crystals of 2-undecanone-α-CD-IC are stable to at least 250 °C, they may be melt-processed into polymer fibers, films, and networks that are mobile below this temperature, and thereby confer upon insect repellency. Further, insecticidal activity of 2-undecaonone from its α-CD complex shows an excellent repellency that 100% of the cockroaches were repelled for the first 2 days after application.

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