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PREPARATION AND STABILITY OF IODINE/α-CYCLODEXTRIN INCLUSION COMPLEX

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ABSTRACT

Inclusion complexes of iodine and α-cyclodextrin were prepared using the coprecipitation method. The complexes obtained were characterized in their solid state using differential scanning calorimetry and in their liquid phase using spectrophotometry, titrimetry and electrochemistry assays. The inclusion and preparation yields were determined. The 1:1 stoichiometry ratio of the inclusion compound was estimated on the basis of the inclusion yield. After optimization of the parameters of the laboratory assays, a scale-up experiment for the complex preparation was carried out. Stability studies showed that, after 16 months preservation, the inclusion complex remained quite stable and suitable for industrial scale-up according to a number of conditions.

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INTRODUCTION

Iodine is frequently used as a reagent in the laboratory and in the dye industry or for its antiseptic properties. Unfortunately it has a lot of drawbacks :

- crystals have heterogeneous shapes, irregular size distribution and sublimate at the surrounding temperature. Moreover iodine is very poorly soluble in water.
- crystals as well as vapours are aggressive. They can cause serious burns, allergic reactions or major disorders in the thyroid function.
- conservation, handling and dissolution of the iodine crystals are difficult.

These problems can be avoided by the inclusion of iodine in α-cyclodextrin. In fact cyclodextrins are able to stabilize hydrophobic molecules in certain steric and energetic circumstances (1,2,3).

Numerous studies of inclusion compounds of iodine in α-cyclodextrin have already been described in the literature. Originally the aim of the authors was often to find a model to understand the formation of the blue complex of starch/iodine. Separation troubles of the cyclodextrin from starch have certainly led many authors to describe the orange α-cyclodextrin/iodine complex as a blue complex (4,5). Both crystallographic studies in the solid state (6,7,8) and studies in solution (9,10,11,12) allowed the determination of the crystal structure, the complex stoichiometry, and the stability constant of the complex. Other authors have shown an interest in the hydrolysis of iodine into polyiodides (13,14) and in the electrical properties of the polyiodides/α-cyclodextrin inclusion compounds themselves (15). In 1976, Japanese patents were registered (16), that describe the preparation of an iodine/beta-cyclodextrin complex used as an antiseptic and antifungal agent or as a food preservative.

Nevertheless the purpose of this work is not a fundamental study of α–cyclodextrin/iodine complexes but a useful approach with two main goals : on the one hand different preparation methods are

discussed leading to stable complexes, easy to handle and, on the other hand, a suitable apparatus for industrial preparation of the inclusion compound is proposed.

After optimization of the preparation parameters on the laboratory scale, a scale-up experiment was carried out followed by a time course stability study of the iodine/α-cyclodextrin complex.

MATERIALS AND METHODS

Iodine crystals, solvents (ethanol, diethylether, methylene chloride) and perchloric acid were purchased from Prolabo (France), and α-cyclodextrin from Chinoin (Hungary).

Alpha-cyclodextrin was first dissolved in acidified distilled water (pH 3, perchloric acid) in order to avoid iodine hydrolysis (17). Crystals or organic solution of iodine were added to the aqueous solution of α-cyclodextrin and the mixture was stirred. The coprecipitate obtained is filtered, purified with diethylether, dried and ground in a mortar. The inclusion complex was characterized as a fine orange powder.

Laboratory assays were first performed with 40 ml of an α-cyclodextrin solution. The scale-up experiment needed 1000 ml for batch A and 420 ml for batch B. The stirring of the media was obtained using magnetic stirrers during the laboratory assays while anchor-shaped and propeller-shaped stirrers were used respectively for batches A and B (Table 1).

TABLE 1

Preparation parameters of batches A and B

	batch A	batch B
mixture volume (ml)	1000	420
stirring agitator	anchor-shaped	propeller-shaped
shape of the container	cylindrical, ending with a little pit	spherical
filtration	Büchner system	filter paper
drying	vacuum	oven 40/50 °C

Coprecipitation containers were made of glass. The batch A container was cylinder-shaped, with a small pit at the bottom, and the batch B container was spherical. All the laboratory experiments were carried out in flat-bottomed flasks.

The solid state of the inclusion compounds of laboratory assays and batch B were obtained by filtration using filter paper. The solid complexes were then dried in an oven at 40/50 °C for 12 to 24 hours. For batch A, the coprecipitate was filtered using a Büchner system and dried under vacuum.

Different analytical methods were carried out for the evaluation of iodine in the inclusion complex. Titrimetric assays were achieved using sodium thiosulphate (18). UV visible spectra (from 220 to 550 nm) were recorded using a Perkin-Elmer Lambda 5 Spectrophotometer. A Tacussel R PRGE potentiometer (rotating Pt tell-tale electrode 3 cm^2, auxiliary Pt electrode, Ag/AgCl reference electrode) was used for the electrochemistry assay. Differential scanning calorimetry analyses were carried out with a Dupont Instrument 910 DSC (scan rate equal to 10 °C/min).

Batches of laboratory assays and batch B were stored respectively for 16 and 14 months in small flasks made of plain glass and closed using rubber stoppers.

Two types of yields were evaluated. The *Preparation Yield* (Yp) represents (in percent) the quantity of inclusion compound obtained with respect to the quantities of raw materials employed. The *Inclusion Yield* (Yi) represents the number of iodine molecules included in 100 molecules of α-cyclodextrin. Yi is equal to 100% for a 1:1 stoichiometry complex.

RESULTS AND DISCUSSION

Inclusion

Three methods were used for the characterization of the inclusion of iodine in the cavity of α-cyclodextrin.

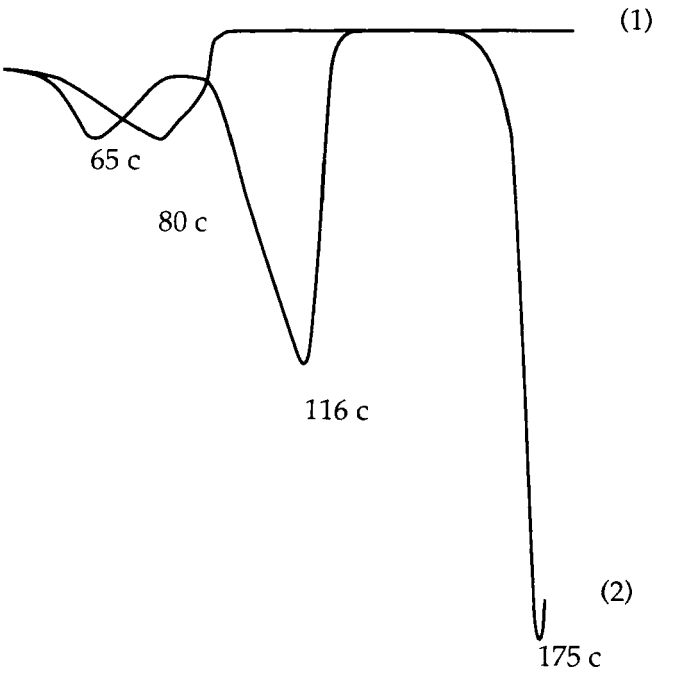

FIGURE 1
Differential scanning calirometry analysis of iodine (1) and iodine/α-cyclodextrin complex (2)

The DSC curves of I_2/α-cyclodextrin complexes failed to show a characteristic endotherm of sublimated iodine at 80 °C. The endotherm peak at 175 °C corresponds to the degradation of the I_2/α-cyclodextrin complex (Figure 1).

UV visible spectra showed a blue shift of the absorbence maximum of iodine from 457 to 444 nm (molar ratio iodine/α-cyclodextrin is equal to one). This hypsochromic effect (19, 20) results from the iodine complexation with α-cyclodextrin (Figure 2).

Intensity/potential curves showed a 30% decrease in the limiting intensity due to the modification of the diffusion coefficient of iodine in the complexed form. A cathodic shift (20 mV) of the half-wave potential is also seen (Figure 3) as observed by Diard *et al* (11).

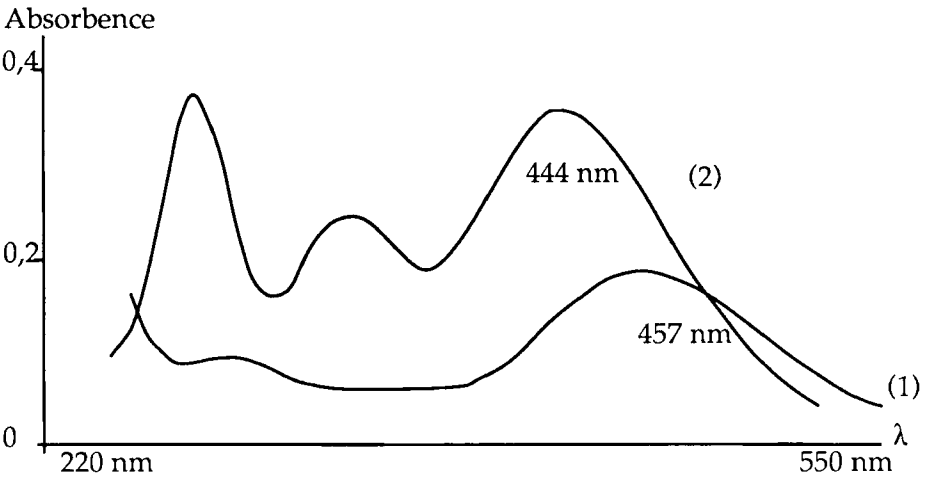

FIGURE 2
Ultraviolet-visible spectra of iodine (1) and iodine/α-cyclodextrin complex (2) in water

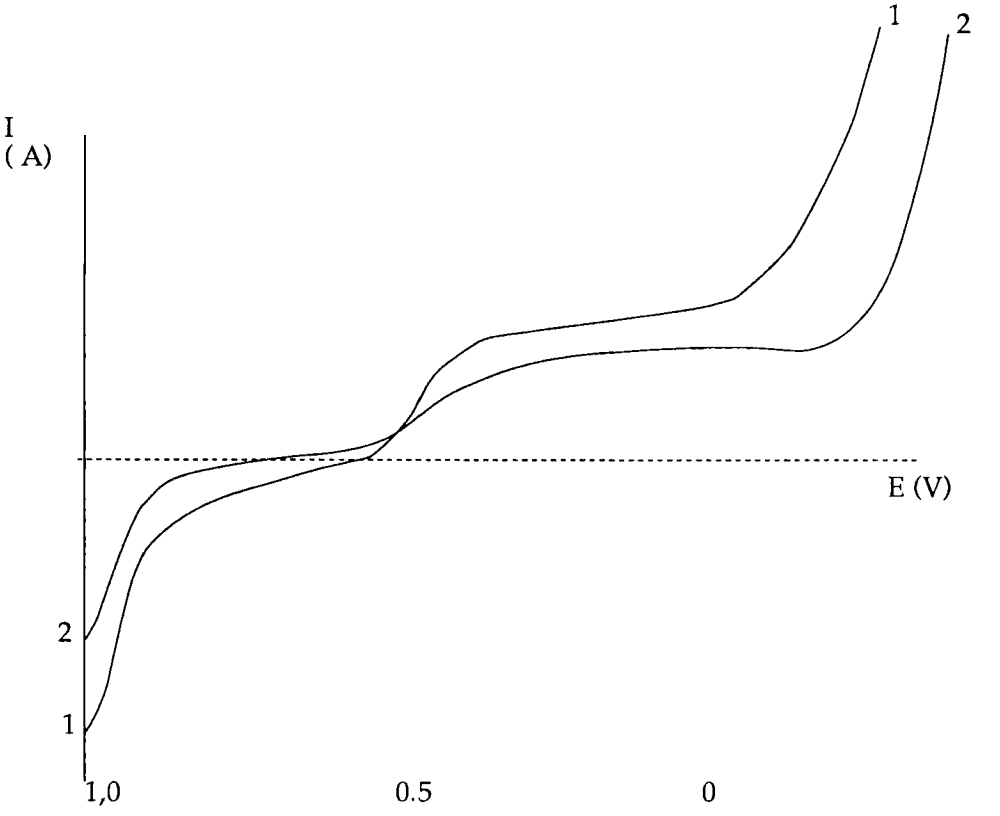

FIGURE 3
Intensity/potential curves of iodine (1) and iodine with α-cyclodextrin (2)

Stoichiometry

The complex stoichiometry was estimated from the results of the titrimetric assays of the laboratory assay batches (the photometric assay gives identical results). According to the definition of the inclusion yield (Yi equal to 100% with 1:1 stoichiometry complex), the mean Yi corresponding to all samples is **94.3 +/- 1.7%**. This value is very close to 100% with respect to the standard deviation commonly observed for titrimetric assays. The stoichiometry of the I_2/α-cyclodextrin complex was then 1:1.

Optimization of the preparation parameters

Previous studies showed that the results of the preparation yields varied between **42.6** and **93.1%** for the laboratory assays (21,22). In agreement with these results and with the observations made during the preparation process, the optimized parameters were designed for scale-up experiment (batches A and B) as described below.

Ground iodine crystals were used for these two assays and were added directly in an aqueous solution of α-cyclodextrin. In fact the use of an organic solution of iodine (in methylene chloride or ethanol) led to a heterogenous product (orange and brown in colour) or (in diethylether) to preparation yields below 80%. In addition it must be stressed that the use of organic solvents has to be avoided in industry (fire hazard, toxicity...).

The α-cyclodextrin concentrations were 0.025 and 0.1157 M for the laboratory assays. A concentration equal to 0.1157 M was chosen for the scale-up experiment because it is close to the α-cyclodextrin solubility at 25 °C. In these conditions, the preparation yields exhibited an improvement (21, 22).

The iodine/α-cyclodextrin molar ratio of the scale-up experiment was chosen equal to 1 because there were no Yp differences when using the ratios 1 and 1.15 during the laboratory assays.

These first assays were performed at 15 and 30 °C. This last temperature was chosen for the scale-up assays. Iodine solubility was higher at 30 °C and the complex precipitation easier.

TABLE 2

Preparation and inclusion yields of the fresh complexes

to time	laboratory assays	batch A	batch B
Yp (%)	42.6 to 93.1	20	71
Yi (%)	94.3 ± 1.7	89.4	95.1

Finally increasing the period of the stirring time (0.5 to 6 days) showed no differences in the Yp values. A one day stirring period was then chosen for the scale-up experiments.

Nevertheless the preparation yields of batches A and B, respectively equal to **20** and **71%**, were less satisfactory (Table 2). The preparation yield value of batch B was due to the adherence of a part of the iodine crystals to the container wall. Concerning batch A, the container and stirring systems were not suitable. Iodine crystals trapped in the pit at the container bottom did not interact with the α-cyclodextrin. This phenomenon explains the dramatic Yp drop, and shows the importance of the effect of the shape of the container on the preparation yield.

The Yi values measured for the scale-up batches were respectively **89.4** and **95.1%** for batches A and B (Table 2). The drop in inclusion yield of batch A could be due to the vacuum drying process. The slow elimination of residual water may contribute to the "disinclusion" of iodine from the α-cyclodextrin cavity. This phenomenon was also observed when the coprecipitate is dried in an oven at 35 °C. A fast drying process at a temperature over 40 °C was shown to be more suitable.

Time stability of the inclusion complex

The stability studies were achieved with 6 laboratory batches for 16 months, and with batch B for 14 months. Except for the container, all these batches were prepared in the same conditions. The stability of the

TABLE 3

Inclusion yields over time (n=number of assays)

inclusion yields over time	storage assays (n=6)	batch B
Yi at To (%)	94.1 ± 1.8	95.1
Yi at T3 (%)	94.9 ± 1.9	/
Yi at T16 (%)	95.4 ± 1.3	(T14) 96.2

complexes was evaluated by looking at the macroscopic appearance, performing differential scanning calorimetry analyses, and determining the inclusion yields.

For all the batches, we observed no modification of the orange complexes. In addition no reddish or silver coloration due to iodine vapours of flasks and rubber stoppers occured. This effect means that the iodine molecules remained stable in the cavity of α-cyclodextrin.

The DSC thermographs performed on the samples were identical to those obtained with fresh inclusion complexes. This means that no crystalline rearrangement occurs during 16 months of storage.

Table 3 shows the determination of the inclusion yields using titrimetric assays after 3 months and 14 or 16 months conservation. No significant differences were observed between the yields of the stored batches and those of the fresh complex batches.

Finally, the stability studies showed that , under these storage conditions, the iodine/α-cyclodextrin inclusion complexes remained stable during at least 14 to 16 months.

CONCLUSION

The preparation of inclusion compounds of iodine and α-cyclodextrin using the coprecipitation method led to a solid product easy to handle. A suitable apparatus was proposed for the scale-up

preparation. Finally a storage study showed that iodine remains stable in the complex at room temperature during at least 16 months.

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