Captisol®: an efficient carrier and solubilizing agent for essential oils and their components

Miriana Kfouri1 | J.D. Pipkin2 | Vince Antle2 | Sophie Fourmentin1 *

1Unité de Chimie Environnementale et Interactions sur le Vivant (UCEIV, EA 4492), SFR Condorcet FR CNRS 3417, ULCO, F-59140 Dunkerque, France
2Ligand Pharmaceuticals Inc., San Diego, California, USA

Correspondence
Sophie Fourmentin, Unité de Chimie Environnementale et Interactions sur le Vivant (UCEIV, EA 4492), SFR Condorcet FR CNRS 3417, ULCO, F-59140 Dunkerque, France. Email: lanotte@univ-littoral.fr

Abstract
Essential oils (EOs) and their individual components have several biological properties and are used in cosmetics, food and pharmaceutical industries. However, their application still presents a challenge owing mainly to their volatility and their poor aqueous solubility and stability. The aim of this study was to evaluate, for the first time, the ability of Captisol® (sulfobutylether-β-cyclodextrin, SBE-β-CD) and Captisol-G® (sulfobutylether-γ-cyclodextrin, SBE-γ-CD) to encapsulate the main volatile components of six essential oils (EOs), to enhance the aqueous solubility of these EOs and to generate controlled release systems. The performance of these CDs was compared to hydroxypropyl-β-cyclodextrin (HP-β-CD) and γ-cyclodextrin (γ-CD), respectively. Formation constants (Kf) of the 40 inclusion complexes were determined by Static Headspace-Gas Chromatography (SH-GC). Then, Total Organic Carbon (TOC) was used to explore and quantify the efficiency of Captisol® and HP-β-CD to enhance the solubility of the six EOs. Finally, multiple headspace extraction (MHE) was applied to perform release studies. Kf values underlined the best binding potential of Captisol® towards all guests. Phase solubility diagrams showed that both Captisol® and HP-β-CD greatly increased the apparent solubility of EOs. The solubilizing potential was inversely proportionate to the EOs intrinsic solubility (Sc). Results indicated that Captisol® can successfully encapsulate EOs, increase their apparent aqueous solubility and decrease their release kinetics. Thus, Captisol® could be considered as a promising carrier to enlarge the application of EOs and their components.

KEYWORDS
Captisol®, cyclodextrins, essential oils, phase solubility, Total Organic Carbon

1 | INTRODUCTION

Essential oils (EOs) and their individual components are generally recognized as flavouring and fragrance agents in cosmetics and food industries. They can also be used in pharmaceutical and medical applications for their antioxidant, antimicrobial and anti-inflammatory activities or to neutralize undesirable taste of bitter drugs. EOs and their components are well accepted by consumers due to their natural origin and nutraceutical potential. However, a major issue is the low solubility and stability as well as the high volatility of EOs and their components that limit their application in the different fields. Moreover, they do evaporate suggesting a need for encapsulation. A method of enhancing EOs solubility is their molecular encapsulation by cyclodextrins (CDs). CDs are cyclic oligosaccharides derived from enzymatic degradation of starch. They have a truncated shape with a hydrophilic surface and a hydrophobic cavity that allows them to encapsulate guests and form inclusion complexes in solution or in solid state. The most common native CDs are α-, β- and γ-CDs and are made up of six, seven and eight glucosyl units, respectively (Figure 1).

Incorporating EOs as inclusion complexes in cosmetic, food or pharmaceutical formulations present several advantages. CDs might enhance the solubility of EOs and their components thus higher concentrations could be used. Produce easy measurable dosage forms, facilitate their dispersion and protect them from interactions...
with other excipients.\textsuperscript{10} CDs could also retain and allow a controlled release for EOs,\textsuperscript{11,12} offer them thermal, oxidative, light and chemical stability\textsuperscript{13-17} and increase their oral bioavailability.\textsuperscript{18} To the best of our knowledge no previous study attempted to investigate the inclusion complexes of Captisol\textsuperscript{®} (sulfobutylether-β-cyclodextrin, SBE-β-CD) and Captisol-G\textsuperscript{®} (sulfobutylether-γ-cyclodextrin, SBE-γ-CD) with EOs and their components while, compared to native CDs, these CDs exhibit greater water solubility and a more desirable safety profile.\textsuperscript{19}

The aim of the present study was to evaluate the ability of Captisol\textsuperscript{®} and Captisol-G\textsuperscript{®} (Figure 2a) to encapsulate the main volatile components (Figure 2b) (camphene, β-caryophyllene, p-cymene, eucalyptol, estragole, limonene, myrcene, α-pinene, β-pinene and γ-terpinene) of six essential oils (EOs) (Artemisia dracunculus, Citrus reticulata Blanco, Citrus aurantifolia, Melaleuca alternifolia, Melaleuca quinquenervia and Rosmarinus officinalis cineolifera) (Table 1). The determination of the formation constants ($K_f$) was realized using Static Headspace-Gas Chromatography (SH-GC). The performance of these CDs was compared to hydroxypropyl-β-cyclodextrin (HP-β-CD) and γ-cyclodextrin (γ-CD) (Figure 2a), respectively. Phase solubility studies for EOs with Captisol\textsuperscript{®} and HP-β-CD, two of the most used CDs in pharmaceutical formulations, were carried out by Total Organic Carbon (TOC) analysis. Finally, the ability of Captisol\textsuperscript{®} to generate controlled release systems was examined by multiple headspace extraction (MHE).

2 | EXPERIMENTAL

2.1 | Materials
EOs were purchased from Herbes et Traditions (Comines, France). Captisol\textsuperscript{®} (average DS = 6.5) and Captisol-G\textsuperscript{®} (average DS = 4.9) were provided by Ligand Pharmaceuticals Inc. (San Diego, CA, USA). HP-β-CD (average DS = 5.6) and γ-CD were provided by Wacker-Chemie (Lyon, France). Camphene, β-caryophyllene, p-cymene, eucalyptol, estragole, limonene, myrcene, α-pinene, β-pinene and γ-terpinene were purchased from Aldrich (Saint-Quentin Fallavier, France). All products were of analytical grade and were used as received. Ultrapure water was used all over the study.

2.2 | Determination of formation constants ($K_f$)
EO (10 ppm) was added to 10 ml of water or CDs (2mM) aqueous solutions previously introduced in 22 ml headspace glass vials. Vials were then sealed by using a silicone septa and aluminium foil and thermostated at 25 ± 0.1°C. After equilibrium, vials were analysed by SH-GC. Peak areas of each EO component were determined. $K_f$ values were calculated using the rapid method based on the following equation:\textsuperscript{20}

$$K_f = \frac{(A_0/A_{CD})}{[CD]_0^f}$$

(1)

where $A_0$ and $A_{CD}$ stand for the peak areas of each EO component in the absence and the presence of CD, respectively; $[CD]_0^f$ is the initial concentration of CD.

$K_f$ values for the standard guests were determined using a SH-GC titration method using different CD concentrations and a constant guest concentration as described previously.\textsuperscript{15}

All measurements were conducted using an Agilent headspace autosampler and a Perkin Elmer Autosystem XL equipped with a flame ionization detector using a DB624 column gas chromatography. Temperature conditions were set as follows: initial temperature of 50°C for 2 min, increased to 190°C at 5°C/min giving a total runtime of 30 min. Nitrogen was used as carrier vector. Main volatile components in EOs were identified on the basis of GC retention times, determined by using EO standard components in the same conditions.

![FIGURE 2](https://example.com/figure2.png)  | A) Schematic representation of the studied CDs and b) chemical structures of the aroma
TABLE 1 Composition of the studied essential oils

| Botanical name            | Common name | Main components                                      |
|---------------------------|-------------|-------------------------------------------------------|
| Artemisia dracunculus     | Tarragon    | Estragole, β-ocimene, limonene                        |
| Citrus reticulata Blanco  | Mandarin    | Limonene, γ-terpinene, α-pinene, myrcene, β-pinene,  |
|                           |             | terpinolene, p-cymene, α-terpinolene, γ-terpinolene, |
| Citrus aurantifolia       | Lime        | Limonene, γ-terpinene, terpinolene, p-cymene, α-terpineol, linalool, β-phellandrene, sinensal, decanal, octanal, methyl n-ethyl anthranilate |
| Melaleuca alternifolia    | Tea tree    | Terpinene-4-ol, α-terpinene, γ-terpinene, terpinolene, α-pinene, p-cymene, β-phellandrene, limonene, β-myrcene, β-pinene, α-phellandrene, eucalyptol, aromadendrene, δ-cadinene, ledene, bicyclogermacrene, allo-aromadrene, α-gurjunene |
| Melaleuca quinquenervia   | Niaouli     | Eucalyptol, α-pinene, limonene, β-pinene, γ-terpinene, p-cymene, α-terpineol, terpinene-4-ol, linalool, viridiflorol, trans-nerolidol, β-caryophyllene, terpenyl acetate |
| Rosmarinus officinalis Cineoliferum | Rosemary | Eucalyptol, α-pinene, β-pinene, camphene, limonene, β-myrcene, p-cymene, camphor, β-caryophyllene, borneol, α-terpineol, linalool, bornyl acetate |

2.3 | Phase solubility studies

Phase solubility studies were carried out according to the method described by Higuchi and Connors (1965).\(^{21}\) Excess amounts of EO were added to CD solutions at different concentrations ranging from 0 to 40mM. The mixtures were shaken overnight at 25°C and then filtered through a 0.45 μm membrane filter. At each CD concentration, EO’s solubility was determined by TOC using a Shimadzu TOC-V CSH analyser. The calculations of EO solubility were done as described by Kfoury et al. (2016).\(^{22}\) Phase solubility diagrams were obtained by plotting the apparent solubility of the EO as a function of CD concentration. Experiments were done in triplicate.

2.4 | Release studies

The release studies were performed using multiple headspace extraction (MHE). 10 ppm of EOS were placed in 22 ml headspace glass vials containing 10 ml of water or of a 1mM Captisol® solution. After equilibrium, vials were submitted to six successive extractions of their headspace at 60°C and the amount of volatiles present in the gaseous phase was determined using GC. At each time interval (1 h), the remaining percentages of each EO component were determined using the following equation:

\[
\text{remaining EO component (\%)} = \left( \frac{A_t}{A_0} \right) \times 100
\]

(2)

where \(A_t\) and \(A_0\) are the peak area of each EO component at time \(t\) and time 0.

The remaining percentages of free or encapsulated EO were also determined as follows:

\[
\text{remaining EO (\%)} = \left( \frac{\sum A_t}{\sum A_0} \right) \times 100
\]

(3)

where \(\sum A_t\) and \(\sum A_0\) stand for the sum of peak areas of the entire EO at time \(t\) and time 0.

The GC settings were set as described in the section above.

2.5 | Statistical analysis

The solubility values of EOS in the presence of HP-β-CD or Captisol® were compared using Student’s t test. The significance level was set at \(p < 0.05\).

3 | RESULTS

3.1 | Formation constants (\(K_f\))

\(K_f\) is a crucial parameter to bring evidence of the formation and the stability of an inclusion complex in solution. It measures the strength of the interaction between the guest and CD. \(K_f\) values of inclusion complexes between the four hosts (Captisol®, HP-β-CD, Captisol-G®, and γ-CD) and the 10 volatile EO components (camphene, β-caryophyllene, p-cymene, eucalyptol, estragole, limonene, myrcene, α-pinene, β-pinene and γ-terpinene) (Figure 2) were determined by SH-GC. \(K_f\) values were calculated based on the experimental variations of the chromatographic signal of each guest, either directly in the EO (by the rapid method based on equation 1) or as a standard compound (by the titration method), arisen by the presence of CDs. Figure 3 illustrates, as an example, a part of the chromatographic profile of the Tea Tree EO in the presence of HP-β-CD and Captisol®.

The reduction of the chromatographic peak areas of the EO components in the presence of CDs reflects their tendency to form inclusion complexes with CDs. This also revealed that CDs, and particularly Captisol®, can efficiently retain EOS and consequently reduce their volatility. \(K_f\) values for all inclusion complexes were determined either directly in the EOS or for guests as pure standards. Results are listed in Table 2.

It’s worthy to note that the number of glucose units determines the cavity diameter of CDs (Figure 1). Thus, HP-β-CD and Captisol® present the same cavity diameter, narrower than that of Captisol-G® and γ-CD which in turn have identical cavity diameter. Moreover, no \(K_f\) values were previously reported for all the ten guests, neither with
Captisol® nor with Captisol-G®. $K_v$ values obtained in this study for inclusion complexes with HP-β-CD and γ-CD were in good agreement with those from the literature.\textsuperscript{17,23-25}

As we can obviously see in Table 2, $K_v$ values determined by both, the rapid and the titration, SH-GC methods were consistent. Captisol® and HP-β-CD showed better complexation ability than Captisol-G® and γ-CD towards all ten guests reflected by higher $K_v$ values. This is due to the fact that the performance of CDs mainly depends on the geometric complementarity between their cavity and the guest.\textsuperscript{23,26-28} Captisol® showed higher $K_v$ values with all guests as compared to HP-β-CD. In fact, both β-CD derivatives possess an extended hydrophobic cavity compared to the native CD due to the presence of substituents chains (Figure 2a). Nonetheless, the sulfobutyl ether (SBE) chain is longer than the hydroxypropyl (HP). Thus, the SBE chains of Captisol® could probably form additional hydrophobic interactions with guests which reinforce the binding strength.

Conversely, $K_v$ values revealed weaker binding potential of Captisol-G® and γ-CD for all guests. Only β-caryophyllene, a bicyclic sesquiterpene, is well recognized by Captisol-G® and γ-CD. This bulky compound fits better into the cavity of γ-CD and its derivatives than linear or monocyclic compounds.\textsuperscript{26}

For all aromas, Captisol® and HP-β-CD showed better complexation ability than Captisol-G® and γ-CD with Captisol® being the most efficient. These results indicated that Captisol® could be considered as an encouraging candidate to formulate aroma inclusion complexes for pharmaceutical applications.

### 3.2 Phase solubility studies

The studied EOs are very complex mixtures and present a large variety of components (Table 1). Their components belong to monoterpenes and sesquiterpenes subfamilies. They present a wide variety of chemical structures. They are hydrocarbons, oxygenated or nitrogen compounds and possess an aliphatic, cyclic or bicyclic structure. Phase solubility studies were performed for the six EOs with Captisol® and HP-β-CD. CD concentrations varied from 0 to 40mM. The TOC measurements and solubility calculations were performed as described by Kfoury et al. (2016).\textsuperscript{22} Phase solubility profiles were plotted and the increases in the apparent EO aqueous solubility were calculated. An example of phase solubility diagrams for rosemary EO with Captisol® and HP-β-CD is illustrated in Figure 4.

EOs presented different intrinsic solubilities ($S_{EO}$) in pure water due to their varied composition. The aqueous solubility of all EOs was improved by the presence of both Captisol® and HP-β-CD. Apparent aqueous solubility of all EOs increased linearly with Captisol® and HP-β-CD concentration giving $A_1$ type profiles. This indicated that both CDs are good solubilizers for EOs. The equations and correlation coefficients that describe the obtained phase solubility profiles as well as the solubility enhancement ratios ($S/S_{EO}$) of EOs at the higher CD concentration are tabulated in Table 3.

At each CD concentration, values obtained for HP-β-CD and Captisol® were compared using statistical analysis. No significant differences were found for the two CDs ($p < 0.05$). Despite that Captisol® showed higher binding affinity (higher $K_v$ values) than

### Table 2

| Compound    | Captisol® | HP-β-CD | Captisol-G® | γ-CD |
|-------------|-----------|---------|-------------|------|
| Camphene    | 4501 (4616)* | 2447, 3033*, 2556b | 1143 (555) | 647, 360°, 389b |
| β-Caryophyllene | 11598 (11115) | 4158, 4904°, 4941b | 3103 (2014) | 3439, 3581°, 4004b |
| α-Pinene    | 1166 (916) | 760, 575°, 817° | 73 (52) | 126, 138°, 172b |
| β-Pinene    | 1092 (1633) | 1311, 1637°, 1361, 1842 | 152 (84) | 217, 214°, 223b |
| Eucalyptol  | 1671 (1479) | 2729, 2787°, 3076b | 102 (51) | 83, 108° |
| Estragole   | 4125 (4069) | 1435, 1581d          | 70 (20)       | 70, 116°, 130b |
| Limonene    | 550 (5035) | 1644, 1742°, 1671° | 316 (260) | 404, 633°, 417b |
| γ-terpinene | 2512 (2456) | 1686, 1554°, 1406b | 75 (45)       | 80, 86°, 40b |

*Data between brackets refer to $K_v$ values determined for aroma as standards using the titration method:
\textsuperscript{a23, b24, c25, d17}
FIGURE 4 Phase solubility profiles of rosemary EO with Captisol® and HP-β-CD

HP-β-CD, both CDs displayed the same behaviour as EO solubilizers. This could be due to that both CDs have the same cavity diameter and a resembling average of DS giving them a close potential of solubilization. In fact, the solubilizing effect is not only due to the formation of inclusion complexes but it also combines several phenomena such as self-association of poorly soluble guests and CD/guest complexes, as well as non-inclusion interactions and micelles formation.9 
Thus, the solubilizing effect is not specific. The solubility enhancement (S/SEO) varied from 5 to 99-fold depending on the EO (Table 3). Moreover, the solubilizing potential of both CDs was inversely proportionate to the EOs intrinsic solubility (Log (S/SEO) = -0.84 Log (S0) + 3.71; R² = 0.97 for Captisol® and Log (S/SEO) = -0.79 Log (S0) + 3.53; R² = 0.95 for HP-β-CD where S0 is the intrinsic solubility of EOs and S is the solubility of EOs in the presence of the highest concentration of each CD). These results are consistent with previous results found for other EOs and flavours with HP-β-CD.8,22

3.3 | Release studies

Captisol® showed higher Kf values with all guests as compared to HP-β-CD. Consequently, the release studies were performed with this CD. The release experiments were carried out at 60°C using MHE for a fixed amount of each EO in the presence and absence of 1mM Captisol®. The release rate constants were then calculated for all EOs and for their main individual components in the presence or absence of 1mM Captisol®. All EOs and their individual components showed first-order release kinetics. Results are summarized in Table 4 and illustrated for Mandarin EO, as an example, in Figure 5.

We could notice from Figure 5 and Table 4 that encapsulation in Captisol® reduced the volatility of EOs and EOs components and allowed their sustained release. At each time interval, the remaining amount of each EO and EO component in the Captisol® solution was considerably higher than that in the free form. The decreases in the release rates of the entire EOs were equivalent to 2.22, 2.25, 2, 2.79, 3.03 and 2.94-fold for Niaouli, Tea Tree, Tarragon, Rosemary, Lime and Mandarin EO, respectively.

In their free form, the common components of different EOs were released at a very similar rate. This outlined the intrinsic chemical of the volatility of each EO component and indicated that the interference of the EO matrix was negligible. The kinetics rate of EO

TABLE 3 Equations, correlation coefficients (R²) of the phase solubility profiles of EOs with Captisol® and HP-β-CD and solubility enhancement ratios S/SEO

| EO       | Captisol® | HP-β-CD |
|----------|-----------|---------|
| **Tarragon** | Y = 0.24X + 0.86 | S/SEO 24 |
| **Mandarin** | Y = 0.39X + 0.18 | 87      |
| **Lime** | Y = 0.23X + 0.09 | 99      |
| **Tea tree** | Y = 0.50X + 4.28 | 8       |
| **Niaouli** | Y = 0.32X + 4.37 | 5       |
| **Rosemary** | Y = 0.31X + 2.86 | 6       |

| Equation | R² | S/SEO |
|----------|----|-------|
| Y = 0.24X + 0.83 | 0.992 | 23    |
| Y = 0.40X + 0.18 | 0.996 | 87    |
| Y = 0.18X + 0.09 | 0.989 | 75    |
| Y = 0.54X + 4.06 | 0.992 | 8     |
| Y = 0.33X + 4.13 | 0.994 | 5     |
| Y = 0.29X + 2.55 | 0.996 | 6     |

TABLE 4 Release rate constants (h⁻¹) for free and Captisol® encapsulated EOs and their main volatile components

| Release rate constants (h⁻¹) | Niaouli | Tea tree | Tarragon | Rosemary | Lime | Mandarin |
|-----------------------------|---------|----------|----------|----------|------|----------|
| Camphene                    | -       | -        | -        | -        | -    | -        |
| β-Caryophyllene             | 0.45    | 0.10     | 0.18     | 0.086    | -    | -        |
| α-Cymene                    | 0.024   | 0.010    | -        | -        | -    | -        |
| Estragole                   | -       | -        | 0.053    | 0.038    | -    | -        |
| Limonene                    | -       | -        | 0.20     | 0.072    | -    | -        |
| Myrcene                     | 0.23    | 0.11     | 0.20     | 0.10     | 0.18 | 0.087    |
| α-Pinene                    | 0.19    | 0.053    | 0.12     | 0.038    | 0.13 | 0.23     |
| β-Pinene                    | 0.19    | 0.052    | 0.13     | 0.038    | -    | 0.13     |
| γ-Terpinene                 | 0.25    | 0.092    | 0.21     | 0.094    | -    | -        |
| Total EO                    | 0.10    | 0.045    | 0.16     | 0.071    | 0.11 | 0.12     |

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components are in good agreement with those previously found in S. Montana EO.\(^{24}\)

Furthermore, the concentration of the component in the EO does not seem to influence its release rate. As an example, the release rates of limonene are 0.21 and 0.20 h\(^{-1}\), respectively in lime (40.56\%) and tarragon (2.23\%) EOs. The same conclusion is made in the presence of CD. However, the release rate of limonene and myrcene are very close in their free form, while the release rate of limonene was slower in the presence of Captisol\textsuperscript{®}. This difference could be explained by the higher formation constant (K\textsubscript{f}) of Captisol\textsuperscript{®}/limonene compared with Captisol\textsuperscript{®}/myrcene (4125 M\(^{-1}\) and 1116 M\(^{-1}\), respectively). These results proved that Captisol\textsuperscript{®} could be considered as an efficient material to retain EOs and insure their sustained release.

\section*{4 | CONCLUSION}

Results showed that Captisol\textsuperscript{®}, Captisol-G\textsuperscript{®}, HP-β-CD and γ-CD could successfully form inclusion complexes with camphene, β-caryophyllene, \(\alpha\)-cymene, eucalyptol, estragole, limonene, myrcene, \(\alpha\)-pinene, \(\beta\)-pinene and \(\gamma\)-terpinene. Captisol\textsuperscript{®} showed the best binding ability as indicated by the highest K\textsubscript{f} values. Moreover, phase solubility studies revealed that Captisol\textsuperscript{®} and HP-β-CD could efficiently enhance apparent aqueous solubility of the studied EOs (Artemisia dracunculus, Citrus reticulata Blanco, Citrus aurantifolia, Melaleuca alternifolia, Melaleuca quinquenervia and Rosmarinus officinalis cineoliferum). All phase solubility diagrams were classified as A\textsubscript{c} type and no significant differences were found between Captisol\textsuperscript{®} and HP-β-CD. Finally, results demonstrated that Captisol\textsuperscript{®} delays the release of EOs and allows the generation of controlled release systems. Altogether results indicated that Captisol\textsuperscript{®} could be seriously considered as a potential carrier and solubilizing agent for EOs and their components.

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