Use of Cyclodextrins as a Cosmetic Delivery System for Fragrance Materials: Linalool and Benzyl Acetate

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Ulya Numanoğlu,[1] Tangül Şen,[1] Nilüfer Tarimci,[1] Murat Kartal,[2] Otilia M.Y. Koo,[3] and Hayat Önyüksel[3]

[1]Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100 Ankara, Turkey
[2]Ankara University, Faculty of Pharmacy, Department of Pharmacognosy, 06100 Ankara, Turkey
[3]University of Illinois at Chicago, Department of Biopharmaceutical Sciences, Chicago, IL 60612

ABSTRACT

The aim of this study was to increase the stability and water solubility of fragrance materials, to provide controlled release of these compounds, and to convert these substances from liquid to powder form by preparing their inclusion complexes with cyclodextrins (CDs). For this purpose, linalool and benzyl acetate were chosen as the fragrance materials. The use of β-cyclodextrin (βCD) and 2-hydroxypropyl-β-cyclodextrin (2-HPβCD) for increasing the solubility of these 2 fragrance materials was studied. Linalool and benzyl acetate gave a B-type diagram with βCD, whereas they gave an A_L-type diagram with 2-HPβCD. Therefore, complexes of fragrance materials with 2-HPβCD at 1:1 and 1:2 molar ratios (guest:host) were prepared. The formation of inclusion complexes was confirmed using proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and circular dichroism spectroscopy. The results of the solubility studies showed that preparing the inclusion complex with 2-HPβCD at a 1:1 molar ratio increased the solubility of linalool 5.9-fold and that of benzyl acetate 4.2-fold, whereas the complexes at a 1:2 molar ratio increased the solubility 6.4- and 4.5-fold for linalool and benzyl acetate, respectively. The stability and in vitro release studies were performed on the gel formulations prepared using uncomplexed fragrance materials or inclusion complexes of fragrance materials at a 1:1 molar ratio. It was observed that the volatility of both fragrance materials was decreased by preparing the inclusion complexes with 2-HPβCD. Also, in vitro release data indicated that controlled release of fragrances could be possible if inclusion complexes were prepared.

KEYWORDS: Cyclodextrin, benzyl acetate, linalool, solubility, stability, controlled release, inclusion complex.

Corresponding Author: Nilüfer Tarimci, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ankara, 06100-Tandoğan, Turkey. Tel: 00 90 312 212 68 05 / 2404; Fax: 00 90 312 213 10 81; E-mail: ntarimci@pharmacy.ankara.edu.tr

INTRODUCTION

Perfuming cosmetic products is an important part of meeting consumer requirements. The essential functions of fragrance materials are to provide a pleasant odor, to mask the base smell of the product, and to give the product an identity.[1] However, since fragrance materials are poorly water-soluble or insoluble compounds and usually exist in a liquid state, the perfuming process may be difficult. Although the surfactants used in cosmetic preparations have been regarded as important raw materials in solubilization techniques for many years, their use as solubilizing agents leads to different problems, such as causing cloudiness and turbidity in the transparent formulations, skin irritation, and sensitization to light.[2-4] Furthermore, the amount of fragrance materials in the product rapidly decreases during storage because of their volatility and poor stability. Cyclodextrin (CD) complexation of fragrance materials increases their solubility and reduces or prevents their evaporation. Likewise, through CD complexation it is possible to obtain controlled release of fragrances.[5] The interaction of the guest with CDs produces a higher-energy barrier to overcome volatilization, thus producing long-lasting fragrances.[6]

CDs are cyclic oligosaccharides consisting of α-(1,4) linked D(+)-glucopyranose units with a relatively hydrophobic central cavity and a hydrophilic outer surface.[7,8] In aqueous solutions, CDs are capable of forming inclusion complexes with various types of lipophilic materials by taking up into the cavity either the whole molecule or some nonpolar part of it.[9,10] These macromolecules and their inclusion compounds have been used in the food, pharmaceutical, and cosmetic industries.[11] In cosmetic formulations, CDs are mainly used (1) to increase the water solubility of lipophilic materials; (2) to convert the liquid or oily materials to powder form; (3) to increase the physical and chemical stability of guest molecules by protecting against decomposition, oxidation, hydrolysis, or loss by evaporation; (4) to provide the controlled release of active ingredients; (5) to reduce or prevent skin irritation; (6) to prevent interactions between various formulation ingredients; (7) to increase or decrease the absorption of various compounds into skin; (8) to stabilize emulsions and suspensions; and (9) to reduce or eliminate undesired odors.[12-16]

The aim of this study was to increase the stability and water solubility of fragrance materials, to provide controlled release of these compounds, and to convert these substances from liquid to powder form by preparing their inclusion complexes with CDs. In this way, the handling properties of fragrance materials in cosmetic formulations can be improved. For this purpose, linalool and benzyl acetate, the fragrance materials, were chosen as examples of terpenic and aromatic compounds, respectively.

Materials and Methods

Materials

β-cyclodextrin (βCD) was kindly provided by Cyclolab (Budapest, Hungary). 2-Hydroxypropyl-β-cyclodextrin (2-HPβCD) (degree of substitution ~0.6) was purchased from Fluka (Buchs, Switzerland). Linalool and benzyl acetate were purchased from Aldrich (Steinheim, Germany) and Merck (Darmstadt, Germany), respectively. All other solvents were of analytical reagent grade.

Determination of Fragrance Materials by High-Performance Liquid Chromatography

The assays for linalool were performed with a high-performance liquid chromatography (HPLC) system consisting of an HP 1100 model G1311A pump and an HP 1100 model G1314A UV detector (Agilent Tech, Waldbronn, Germany). For benzyl acetate, the HPLC system consisted of a Shimadzu model LC-10 AD pump and a Shimadzu model SPD-M 10 AVP diode array detector (Kyoto, Japan). Samples were injected with a 7725 Rheodyne injector system with a 20-μL sample loop. Separation was performed using a HI CHROM C18 (5 μm, 250 × 4.6 mm) column (Berkshire, UK) at ambient temperature. HPLC analyses were performed by isocratic elution at a flow rate of 1.0 mL/min. The mobile phase composition was methanol:water (8:2 vol/vol). All solvents were filtered through a 0.45-μm cellulose acetate membrane filter before use and degassed in an ultrasonic bath.

Dimethyl sulfoxide (DMSO) was chosen as the solvent for the samples prepared with βCD and fragrance materials, whereas methanol was chosen for those prepared with 2-HPβCD and fragrance materials. For both of the fragrance materials, the quantitative assay and the validation of the assay method were performed in both solvents. The samples diluted with methanol were analyzed at 215 nm for linalool and 257 nm for benzyl acetate, and samples diluted with DMSO were analyzed at 257 nm for linalool and 258 nm for benzyl acetate. Volumes of 20 μL each of prepared solutions and samples were injected into the column. The retention times for linalool were observed to be 5.8 minutes in methanol and 6.9 minutes in DMSO, and for benzyl acetate 3.9 minutes in both solvents. The chromatographic run time was 10 minutes. The peak areas were integrated automatically by a computer software program (HPCORE ChemStation, Agilent Tech, Waldbronn, Germany).

Analytical Validation of HPLC Method

The analytical validation of the HPLC method for the determination of linalool and benzyl acetate was performed. The linearity, accuracy, precision, and limit of detection–limit of quantification (LOD-LOQ) values of the HPLC method were calculated and evaluated.

Phase-Solubility Studies

The phase-solubility studies were performed according to the Higuchi and Connors method.[17] For this purpose, excess amounts of fragrance material (50 mg) were added to 10 mL of aqueous CD solutions at various concentrations (0-25 mM for 2-HPβCD and 0-15 mM for βCD) and stirred with a magnetic stirrer at 200 rpm. The temperature was set at 25°C ± 2°C by a water bath combined with a thermostat. After equilibrium was reached, the samples were filtered through a 0.45-μm membrane filter and diluted. While the samples obtained from the phase-solubility studies performed with fragrance materials and βCD were diluted with DMSO, those obtained from the studies performed with 2-HPβCD were diluted with methanol. The molar concentration of fragrance material was plotted vs the molar concentration of CD, and the phase-solubility diagrams of fragrance materials with both of the CDs were obtained.

Calculation of Complex Stability Constants

The complex stability constants were calculated by using slope values of the straight lines of the phase-solubility diagrams with respect to the following equation, as described in the literature[17]:

$$K_c = \frac{Slope}{(S_O \times (1 - Slope))} \quad (1)$$

where S_O is the solubility of linalool or benzyl acetate in the absence of CD.

Preparation of Inclusion Complexes

The inclusion complexes of fragrance materials with 2-HPβCD at molar ratios of 1:1 and 1:2 (guest:host) were prepared by modifying the method used by Matsuda et al.[2] Exactly 2.5 g of 2-HPβCD was dissolved in distilled water (47 mL) to prepare the aqueous CD solution. Calculated amounts of linalool (0.280 g for 1:1 molar ratio and 0.140 g for 1:2 molar ratio) and benzyl acetate (0.272 g and 0.136 g for 1:1 and 1:2 molar

Table 1. Codes and Ingredients of Gel Formulations*

Ingredients	Formulation Code			
	JL	JLC	JB	JBC
Carbopol 940 (g)	0.5	0.5	0.5	0.5
Triethanolamine (g)	0.5	0.5	0.5	0.5
Ethanol (g)	5	5	5	5
Propylene glycol (g)	2	2	2	2
Linalool (g)	1	—	—	—
Linalool:2-HPβCD (1:1) inclusion complex (g)	—	10.7†	—	—
Benzyl acetate (g)	—	—	1	—
Benzyl acetate:2-HPβCD (1:1) inclusion complex (g)	—	—	—	12.8†
Purified water (g) qs	100	100	100	100

*JL indicates gel formulation containing uncomplexed linalool; JLC, gel formulation containing linalool:2-HPβCD (1:1) complex; JB, gel formulation containing uncomplexed benzyl acetate; JBC, gel formulation containing benzyl acetate:2-HPβCD (1:1) complex; 2-HPβCD, 2-hydroxypropyl-β-cyclodextrin; qs, quantum sufficient.
†The amount of inclusion complex equivalent to 1 g of fragrance material.

ratio, respectively) were gradually added to the aqueous CD solution and mixed with a magnetic stirrer at 300 rpm for 12 hours. The temperature was fixed at 25°C ± 2°C by a water bath combined with a thermostat that was placed on the stirrers. Then the solution was filtered through a 0.45-μm cellulose acetate membrane filter. The aqueous solution of inclusion complex obtained by this procedure was converted to powder form by the lyophilization (freeze-drying) method.

Confirmation of Inclusion Complex Formation

^{1}H-NMR and circular dichroism spectroscopy were used to confirm the inclusion complex formation.

^{1}H-NMR Spectroscopy

^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer (Bruker, Germany) operating at 400 MHz. The samples were prepared by dissolving 2-HPβCD and complexes in heavy water (deutorium oxide [D_2O]).

Circular Dichroism Spectroscopy

Circular dichroism spectra were taken using a Jasco J-710 spectropolarimeter (Jasco, Easton, MD). Samples were diluted with deionized water before analysis, and the concentration of the samples was 1% wt/vol. The following parameters were used in the circular dichroism studies: a circular cell of 0.1 cm path length, a scanning speed of 50 nm/min, a bandwidth of 1.0 nm, a resolution of 1 nm, and ambient temperature.

Determination of Solubilized Fragrance

Solubility experiments were performed in order to determine the water solubilities of fragrance materials and their inclusion complexes at the molar ratios of 1:1 and 1:2. The excess amount of fragrance material (80 mg) or the corresponding amount of the inclusion complex was mixed with distilled water (10 mL) using a magnetic stirrer at 200 rpm and a water bath combined with a thermostat at 25°C ± 2°C. At equilibrium, the samples were filtered, diluted with methanol, and analyzed by HPLC.

Preparation of Gel Formulations

The gel-based moisturizing formulations were prepared using uncomplexed fragrance materials and inclusion complexes (1:1) obtained in powder form. To prepare the gel formulations containing uncomplexed fragrance materials, Carbopol 940 was dissolved in purified water using a propeller-type Stir-Pak mechanical stirrer (Cole-Parmer Ins. Co., Chicago, IL) at 600 rpm. Fragrance material was dissolved in the mixture of alcohol and propylene glycol, and this mixture was added to the Carbopol 940 solution while stirring. Then triethanolamine dissolved in water was poured into this mixture slowly to achieve gel formation through the neutralization process. On the other hand, to prepare the gel formulations of

Table 2. Linearity Results*

	Linalool		Benzyl Acetate	
	Methanol	DMSO	Methanol	DMSO
Equation	$y = 5232x + 91.82$	$y = 12.22x + 2.12$	$y = 1.3 \times 10^6x - 1174$	$y = 1.2 \times 10^6x - 7540$
r^2	0.999	0.999	0.999	0.999
Slope	5232	12.22	1.3×10^6	1.2×10^6
SE	55.74	0.18	5245	1380
CI (95%)	5232 ± 143	12.22 ± 0.43	$1.3 \times 10^6 \pm 1283$	$1.2 \times 10^6 \pm 3376$
Intercept	91.82	2.12	–1174	–7540
SE	36.07	2.60	1324	3484
CI (95%)	91.82 ± 92.73	2.12 ± 6.36	–1174 ± 3241	–7540 ± 8525

*DMSO indicates dimethyl sulfoxide; SE, standart error; CI, confidence interval.

Table 3. Accuracy of the HPLC Method*

	Linalool		Benzyl Acetate	
	Methanol	DMSO	Methanol	DMSO
Theoretical concentration (mg/mL)	0.150	12.50	0.250	0.250
Measured concentration (mg/mL), mean	0.145	12.74	0.249	0.247
Recovery %, mean ± SD	96.8 ± 1.08	101.9 ± 0.543	99.9 ± 0.207	98.6 ± 0.420
RSD % of recovery	1.11	0.53	0.21	0.43

* HPLC indicates high-performance liquid chromatography; DMSO, dimethyl sulfoxide; RSD, relative standard deviation.

inclusion complexes, the inclusion complex was dissolved in purified water first, and then this solution was used to prepare the Carbopol 940 solution. The steps that followed were the same as those used in the above procedure. Codes and ingredients of gel formulations appear in Table 1.

Stability Studies on Gel Formulations

For the stability studies, the gel formulations were stored in a climatic chamber set at 25°C ± 2°C and 50 ± 5% relative humidity. The amount of fragrance material in the gel formulations was determined at 60-day intervals during the 6-month period. The quantification of benzyl acetate and linalool in the gel formulations was performed using HPLC, as described previously.

Release Profiles of Fragrance Materials

The release profiles of fragrance materials from gel formulations were investigated using modified Franz diffusion cells. Exactly 2.5 g of the gel formulation sample was loaded into the donor compartment. Freshly boiled and cooled distilled water was used as the receptor phase, and the temperature of the receptor phase was set at 32°C ± 1°C. The volume of the receptor compartment was 12 mL, and the effective surface area available for diffusion was 1.54 cm^2. As a diffusion membrane, a synthetic cellulose acetate membrane with a pore size of 0.45 μm was used after having been treated with distilled water for 30 minutes. Samples of 0.2 mL were withdrawn from the receptor phase at predetermined time intervals. The samples diluted with methanol were analyzed by HPLC.

Results and Discussion

Analytical Validation of HPLC Method

Linearity and Range

Each of the 8 different concentration standards for each analyte was injected 6 times. The peak areas obtained for the 6 analyses were averaged at each concentration. The average peak areas were plotted vs concentration. A linear response between peak area and concentration for the both of the compounds was observed. Table 2 presents the equations of the regression line, regression coefficients, SEs, and confidence intervals (95%) of the slope and intercept for each compound. Excellent linearity was obtained for linalool between concentrations of 0.003 and 1.5 mg/mL in methanol and 5 and 22.5 mg/mL in DMSO with $r^2 = 0.999$; and for benzyl acetate between concentrations of 0.05 and 0.4 mg/mL in both methanol and DMSO with $r^2 = 0.999$.

Accuracy

Standard working solutions containing linalool and benzyl acetate were prepared, yielding final concentrations of 0.15 mg/mL in methanol and 12.5 mg/mL in DMSO for linalool; and 0.25 mg/mL in both methanol and DMSO for benzyl acetate. The prepared standards were injected 6 times as a test sample. From the respective area counts, the concentrations of the linalool and benzyl acetate were calculated using the detector responses. The accuracy was defined in terms of the relative standard deviation (coefficient of variation) (RSD) of percent recovery values. The results are listed in Table 3. Since the RSD values obtained were less than 2%, the method was deemed to be accurate.

Table 4. Repeatability of the HPLC Method (n = 6)*

	Linalool		Benzyl Acetate	
	Methanol	DMSO	Methanol	DMSO
Theoretical concentration (mg/mL)	0.150	12.50	0.250	0.250
Measured concentration (mg/mL), mean ± SD	$0.139 \pm 7.53 \times 10^{-4}$	12.48 ± 0.207	$0.252 \pm 7.53 \times 10^{-4}$	$0.242 \pm 1.52 \times 10^{-3}$
RSD %	0.54	1.66	0.30	0.63

*HPLC indicates high-performance liquid chromatography; DMSO, dimethyl sulfoxide; RSD, relative standard deviation.

Table 5. Reproducibility of the HPLC Method (n = 6)*

	Linalool				Benzyl Acetate			
	Methanol		DMSO		Methanol		DMSO	
	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Theoretical concentration (mg/mL)	0.150	0.150	12.50	12.50	0.250	0.250	0.250	0.250
Measured concentration (mg/mL), mean†	0.142	0.143	13.10	12.99	0.254	0.253	0.238	0.238
SD ($\times 10^{-3}$)	1.17	0.817	77	99	0.817	0.633	2.16	3.01
RSD %	0.82	0.57	0.58	0.76	0.32	0.25	0.91	1.27

*HPLC indicates high-performance liquid chromatography; DMSO, dimethyl sulfoxide; RSD, relative standard deviation.
†None of the values in this row are significant at $P > .05$.

Precision

The repeatability of the method was checked by the analysis of 6 replicate injections of linalool and benzyl acetate in methanol and DMSO. The repeatability of the method was expressed as the RSD of measured concentrations (Table 4). RSD values were less than 2%.

The reproducibility of the HPLC method was evaluated by carrying out the analysis using standard working solutions on different 2 days. RSD values were less than 2% (Table 5).

LOD was estimated at a signal-to-noise ratio (S/N) of 3. LOQ was estimated at an S/N of 10. LOD and LOQ values were experimentally verified by 6 injections of linalool and benzyl acetate at the LOD and LOQ concentrations. While LOQ values of linalool in methanol and DMSO were found to be 0.003 mg/mL and 1.5 mg/mL, respectively, LOD values were found to be 0.0009 mg/mL and 0.5 mg/mL, respectively. For benzyl acetate in methanol and DMSO, the LOQ value was 0.05 mg/mL, and LOD values were 0.005 mg/mL and 0.0125 mg/mL, respectively.

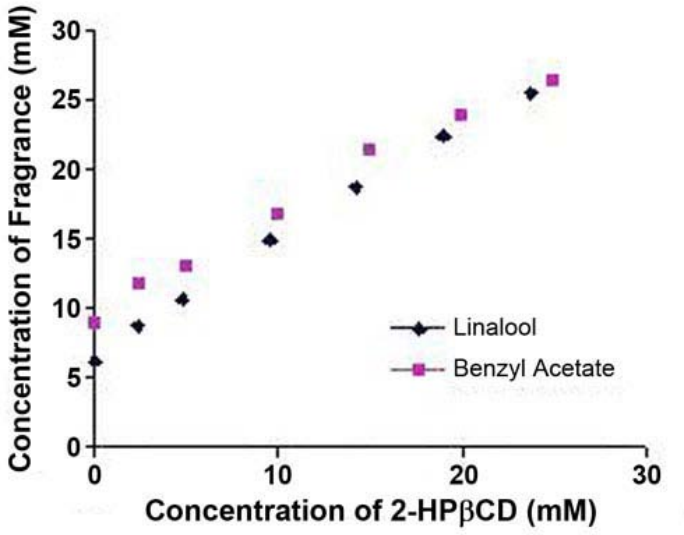

Figure 1. Phase-solubility diagrams of fragrance materials with 2-HPβCD. 2-HPβCD indicates 2-hydroxypropyl-β-cyclodextrin.

Phase-Solubility Diagrams

As a result of the phase-solubility studies, linalool and benzyl acetate were determined to give an A_L-type diagram with 2-HPβCD and a B-type with βCD. Ajisaka et al also have reported that the terpenic fragrance materials gave B-type

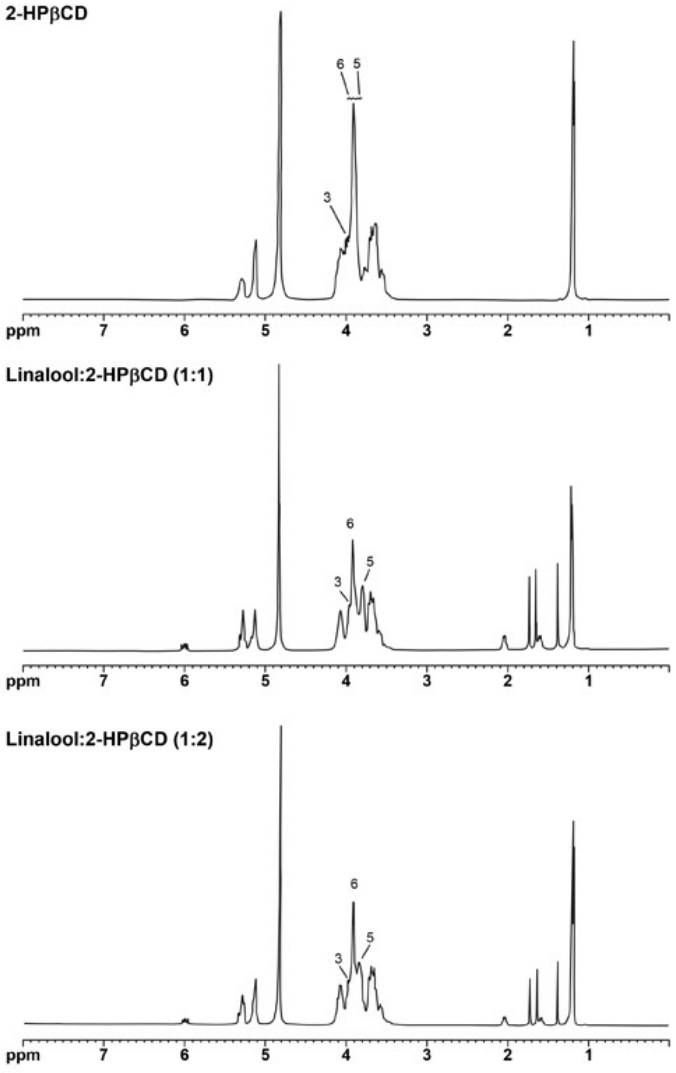

Figure 2. ^{1}H-NMR spectra of 2-HPβCD, linalool:2-HPβCD (1:1), and linalool:2-HPβCD (1:2). 2-HPβCD indicates 2-hydroxypropyl-β-cyclodextrin.

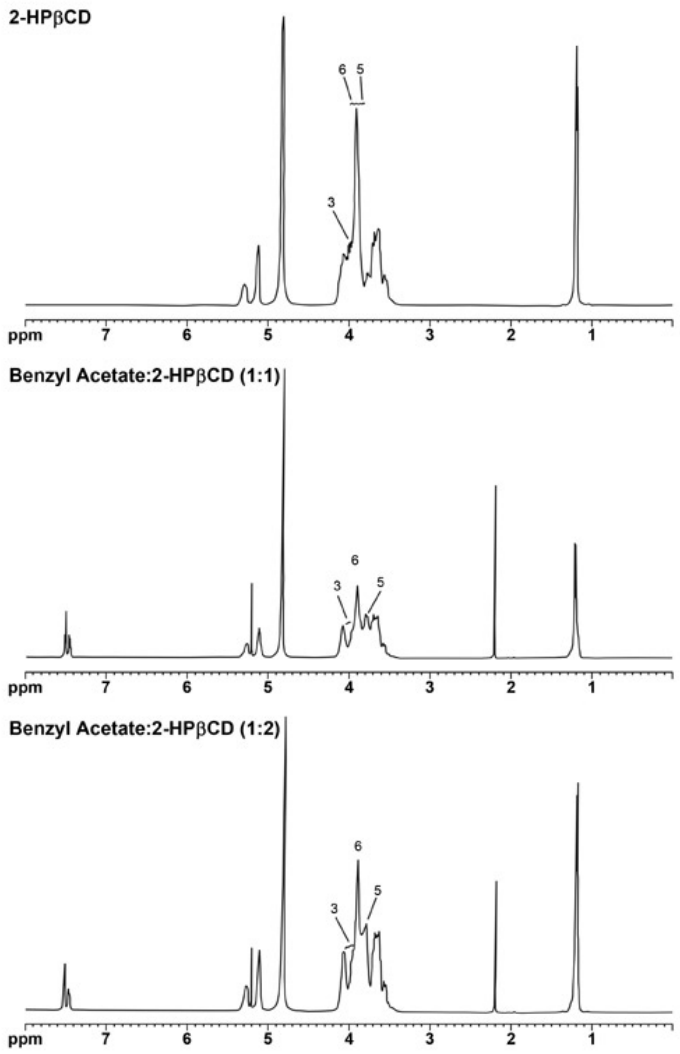

Figure 3. ^{1}H-NMR spectra of 2-HPβCD, benzyl acetate:2-HPβCD (1:1), and benzyl acetate:2-HPβCD (1:2). 2-HPβCD indicates 2-hydroxypropyl-β-cyclodextrin.

phase-solubility diagrams with βCD.[18] Phase-solubility diagrams obtained with 2-HPβCD are seen in Figure 1. The complex stability constants (K_c) of fragrance materials with 2-HPβCD were calculated by using phase-solubility diagrams. The K_c values obtained were 720 M^{-1} and 275 M^{-1} for linalool:2-HPβCD complex and benzyl acetate:2-HPβCD complex, respectively.

Since a B-type phase-solubility diagram shows limited soluble or insoluble inclusion complex formation, the complexes of fragrance materials at molar ratios of 1:1 and 1:2 were prepared with only 2-HPβCD.

Confirmation of Complex Formation by Using ^{1}H-NMR and Circular Dichroism Spectroscopy

^{1}H-NMR Spectroscopy

If the inclusion complex formation indeed occurs, H3 and H5 protons of CD that are directed toward the interior of the CD cavity are significantly shaded by the protons of the guest molecule and shift to a high magnetic field in the ^{1}H-NMR spectrum.[19-24]

^{1}H-NMR spectra showed that the signal of H3 proton, which initially appeared in the spectrum of 2-HPβCD, shifted upfield and interfered with the signal of H6 proton as a result of complexation. Similarly, the signal of H5 proton, which was initially overlapped by the H6 signal, moved to a higher field and became visible in the spectra of complexes (Figures 2 and 3). The chemical shifts (δ ppm) and chemical shift alterations (Δδ ppm) of H3 and H5 protons are seen in Table 6. These results indicate that the inclusion complex formation of fragrance materials with 2-HPβCD indeed occurred.

Circular Dichroism Spectroscopy

The circular dichroism spectra of the inclusion complexes of fragrance materials are shown in Figure 4. In the circular dichroism spectra, the induced optical activity of benzyl acetate and linalool by means of the inclusion complexation with 2-HPβCD was observed. The optical activities of linalool and benzyl acetate (achiral guest molecules) were induced when they were included in the cavity of the chiral HPβCD, and because of the chromophore groups of these guest molecules, absorption bands at around 200 nm were determined in the circular dichroism spectra.

When CD is added to the aqueous solution of an achiral guest, induced Cotton effects will be observed in the circular dichroism spectra because of the induced optical activity of the guest molecule by inclusion in a chiral cavity. The Cotton effect is observed only when the guest molecule or its

Table 6. Chemical Shifts of H3 and H5 Protons in the ^{1}H-NMR Spectrum*

		Linalool:2-HPβCD				Benzyl Acetate:2-HPβCD			
		1:1		1:2		1:1		1:2	
Proton number	2-HPβCD	δ ppm	Δδ ppm	δ ppm	Δδ ppm	δ ppm	Δδ ppm	δ ppm	Δδ ppm
H3	3.9831	3.9648	0.0183	3.9643	0.0188	3.8946	0.0885	3.9568	0.0263
H5	3.9209	3.7920	0.1289	3.8430	0.0779	3.7749	0.1460	3.8004	0.1205

*^{1}H-NMR, ; 2-HPβCD, 2-hydroxypropyl-β-cyclodextrin; δ ppm, chemical shift; Δδ ppm, chemical shift alteration.

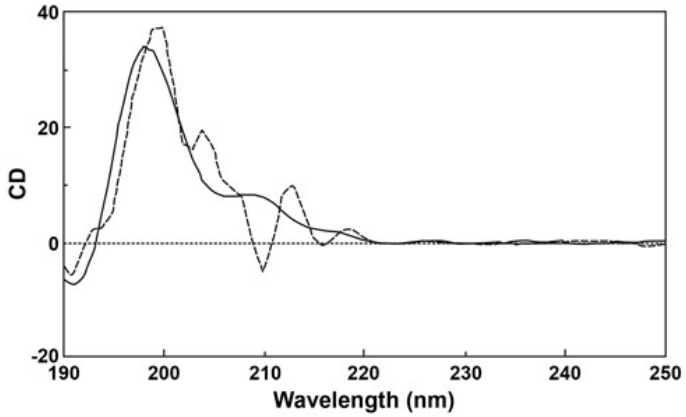

Figure 4. CD spectra of linalool:2-HPβCD (1:1) inclusion complex (——) and benzyl acetate:2-HPβCD (1:1) inclusion complex (- - - -). CD indicates circular dichroism; 2-HPβCD, 2-hydroxypropyl-β-cyclodextrin.

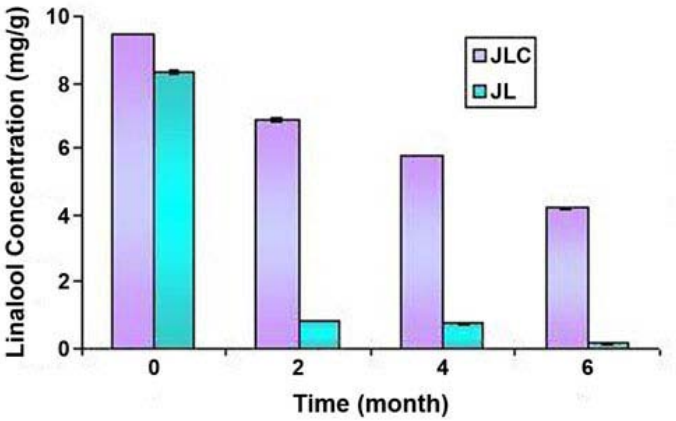

Figure 5. The results of stability studies on JL and JLC. JL indicates gel formulation containing uncomplexed linalool; JLC, gel formulation containing linalool:2-HPβCD (1:1) complex.

chromophore group is actually included in the CD cavity.[25,26] An outer surface association of a guest with the CD molecule may lead to some modification of other spectral properties but not to induced Cotton effects.[26]

Results of Solubility Experiments

The water solubilities of fragrance materials and their inclusion complexes prepared with 2-HPβCD at molar ratios of 1:1 and 1:2 were determined by the solubility studies. The results are shown in Table 7. As seen in Table 7, preparing the inclusion complex with 2-HPβCD at a 1:1 molar ratio increased the solubility of linalool 5.9-fold and that of benzyl acetate 4.2-fold. At a 1:2 molar ratio the water solubility was increased 6.4- and 4.5-fold for linalool and benzyl acetate, respectively.

The results showed that the complexes prepared at a 1:2 molar ratio caused a higher increase in the solubility of fragrance materials, compared with the complexes prepared at a 1:1 molar ratio. This increase was thought to be caused by the free CDs, which did not join in the complex formation, but enhanced the wettability of fragrance materials, as is usually observed in physical mixtures. However, when the possible interactions between an excess amount of CDs and other materials in the cosmetic formulations and the increased costs were considered as well, preparing the complex at a 1:1 molar ratio seemed more favorable. Therefore, the inclusion complex at the molar ratio of 1:1 was used in the gel formulations prepared for the stability and controlled release studies.

Results of Stability Studies

At the end of 6 months, the decrease in the linalool concentration of the gel formulation containing uncomplexed linalool (JL) was 98.2%, while that of the formulation prepared with linalool:2-HPβCD (1:1) complex (JLC) was 55%. In the same period of time, the benzyl acetate concentration of uncomplexed benzyl acetate (JB) and benzyl acetate:2-HPβCD (1:1) complex (JBC) formulations decreased 94.4% and 67%, respectively (Figures 5 and 6). The results of the stability studies on the gel formulations showed that the volatility of both of the fragrance materials was decreased by preparing inclusion complexes with 2-HPβCD.

Release Profiles of Fragrance Materials

The release profiles of fragrance materials from gel formulations consisting of uncomplexed fragrances and inclusion

Table 7. Results of Solubility Experiments (n = 6)*

	Water Solubility (mg/mL)	CI (95%)	SD
Linalool	1.14	1.14 ± 0.024	0.023
Linalool:2-HPβCD (1:1)	6.68	6.68 ± 0.063	0.060
Linalool:2-HPβCD (1:2)	7.26	7.26 ± 0.040	0.040
Benzyl acetate	1.50	1.50 ± 0.020	0.019
Benzyl acetate:2-HPβCD (1:1)	6.31	6.31 ± 0.099	0.094
Benzyl acetate:2-HPβCD (1:2)	6.80	6.80 ± 0.154	0.147

*CI indicates confidence interval; 2-HPβCD, 2-hydroxypropyl-β-cyclodextrin.

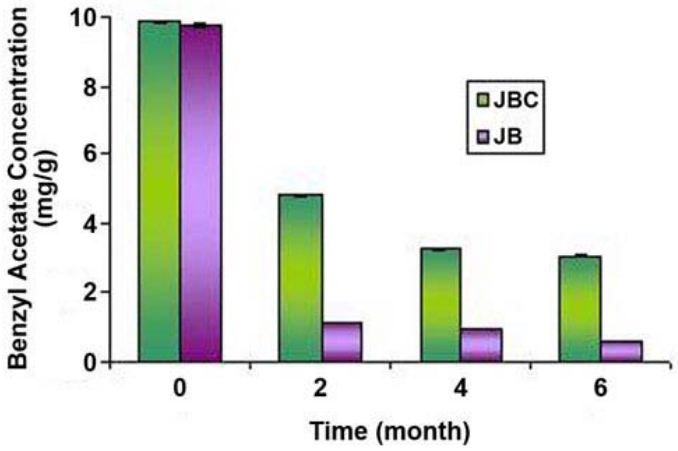

Figure 6. The results of stability studies on JB and JBC. JB indicates gel formulation containing uncomplexed benzyl acetate; JBC, gel formulation containing benzyl acetate:2-HPβCD (1:1) complex.

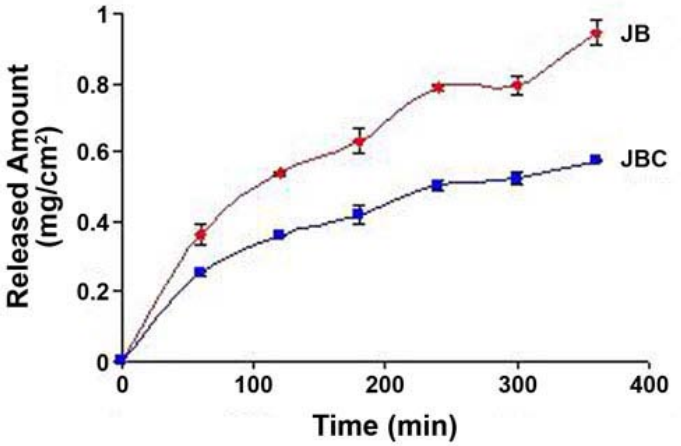

Figure 8. The release profiles of benzyl acetate from JB and JBC. JB indicates gel formulation containing uncomplexed benzyl acetate; JBC, gel formulation containing benzyl acetate:2-HPβCD (1:1) complex.

complexes are given in Figures 7 and 8. The release data were evaluated statistically by Student *t* test using PCS Version 4.1 (New York, NY). It was observed that the amount of fragrance materials released from JBC and JLC was significantly lower than that released from JB and JL ($P < .05$). This indicated that prolonged/controlled release of fragrances could be possible by preparing inclusion complexes. The data obtained from release studies were evaluated kinetically, and fitness to the 3 different kinetic models—zero order, first order, and Higuchi (Q√t)—was investigated. It was found that the release of benzyl acetate and linalool from gel bases complied with the Higuchi (Q√t) kinetic model (Table 8).

CONCLUSION

The inclusion complexes of linalool and benzyl acetate with 2-HPβCD significantly increased the water solubility of these materials. Also, by the complexation process, the liquid fragrance materials could be obtained in powder form, and thus the handling properties of cosmetic formulations could be improved. The controlled release of linalool and benzyl acetate can be achieved by preparing inclusion complexes of these fragrance materials with 2-HPβCD, and the stability of these compounds in the gel formulations can be increased by complexation. As a result, it can be concluded that CDs (especially 2-HPβCD) are very suitable cosmetic delivery systems for fragrance materials.

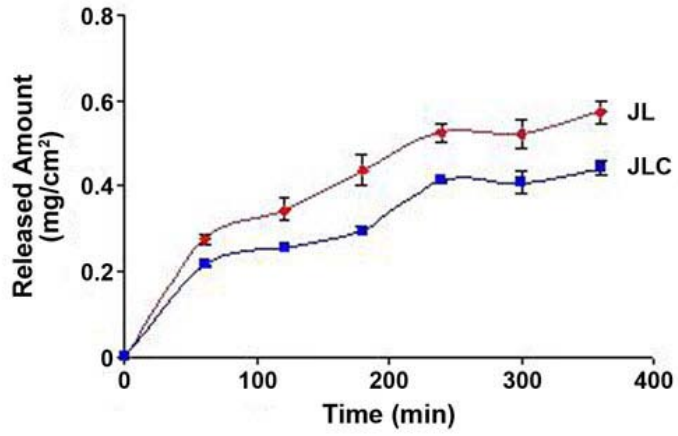

Figure 7. Release profiles of linalool from JL and JLC. JL indicates gel formulation containing uncomplexed linalool; JLC, gel formulation containing linalool:2-HPβCD (1:1) complex.

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Table 8. Kinetic Parameters of Fragrance Release From Gel Formulations*

Kinetic Model		JL	JLC	JB	JBC
Zero order	r^2	0.946	0.953	0.964	0.953
	k_0 (mg h^{-1})	0.002	0.001	0.003	0.002
First order	r^2	0.913	0.924	0.920	0.908
	k_1 (h^{-1})	0.002	0.003	0.003	0.003
Higuchi	r^2	0.997	0.995	0.998	0.999
(Q√t)	k ($h^{-1/2}$)	0.032	0.024	0.048	0.031

*JL indicates gel formulation containing uncomplexed linalool; JLC, gel formulation containing linalool:2-HPβCD (1:1) complex; JB, gel formulation containing uncomplexed benzyl acetate; JBC, gel formulation containing benzyl acetate:2-HPβCD (1:1) complex. r^2 is the determination coefficient, and k_0, k_1, and k are release rate constants.

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