Journal of Inclusion Phenomena and Macrocyclic Chemistry **49**: 275–281, 2004.

Inclusion Complexation of the Sunscreen 2-Hydroxy-4-Methoxy Benzophenone (Oxybenzone) with Hydroxypropyl-β-Cyclodextrin: Effect on Membrane Diffusion

VIKRAM SARVEIYA[1], JOHN F. TEMPLETON[1] and HEATHER A. E. BENSON[2,*]
[1]*Faculty of Pharmacy, University of Manitoba, Manitoba, Canada;* [2]*Western Australian Biomedical Research Institute, School of Pharmacy, Curtin University of Technology, Perth, Western Australia*

(Received: 28 May 2003; in final form: 6 April 2004)

Key words: benzophenone-3, cyclodextrin, oxybenzone, skin penetration, sunscreen

Abstract

It is desirable to minimize skin penetration of some drugs, such as sunscreens and insect repellents. Available *in vivo* and *in vitro* data suggest appreciable absorption of some sunscreen agents. The purpose of this study was to investigate the effect of hydroxypropyl-β-cyclodextrin (HPβCD) on the release and permeation of the sunscreen agent 2-hydroxy-4-methoxy benzophenone (oxybenzone). The interaction between oxybenzone and HPβCD was studied in water by phase solubility analysis. The inclusion complex was characterized by thermal analysis and nuclear magnetic resonance spectroscopy. UV transmittance and percent UVA transmittance, as a preliminary measure of sun protection factor (SPF), were determined. *In vitro* permeation experiments were conducted in Franz-type diffusion cells at 37 °C, using the model membrane poly(dimethyl siloxane) (PDMS) and 4% bovine serum albumin in phosphate buffer solution (pH 7.4) as the receptor phase. HPβCD caused a marked increase in the aqueous solubility of oxybenzone. Data from the phase solubility experiment indicated the formation of 1:1 oxybenzone-cyclodextrin complex. UV transmittance studies indicated that the presence of HPβCD did not suppress the UV absorbing properties of oxybenzone. The release and membrane permeation of oxybenzone was significantly reduced in the presence of equimolar, 2 times molar and 1, 2 and 4% of HPβCD. It is concluded that HPβCD can reduce the release/membrane diffusion of oxybenzone whilst retaining its efficacy as a sunscreen agent. This formulation strategy may be useful in controlling skin penetration of topically applied sunscreens and other chemicals.

Introduction

Increased evidence linking sun exposure with skin aging, damage and development of skin cancers has led to more extensive use of sunscreens in beach products and everyday cosmetics. Sunscreen products are formulated to provide a specific sun protection factor (SPF) and to absorb a broad spectrum of ultraviolet radiation (UVR). Since sunscreens are regularly applied to large areas of the body, it is essential to have an understanding of their safety and minimize absorption of actives to viable tissues.

Acute adverse toxic effects of specific sunscreen agents include contact irritation, allergic contact dermatitis, phototoxicity, photoallergy, and staining of the skin. However, the incidence is relatively small considering their widespread use. Relatively little information is available on the mutagenic and carcinogenic potential of sunscreen agents [1]. It has been suggested that under UVR some sunscreens and related chemicals may have mutagenic effects in the viable tissues of the epidermis and dermis [2]. A recent report that sunscreens caused mitochondrial stress and inhibited growth in cultured human cells has added to safety concerns [3]. Clearly, the best means to ensure sunscreen safety is to minimize penetration to viable tissues.

Ideally a topically applied sunscreen would be localized in the stratum corneum without penetration to deeper viable tissues. This likely occurs in many lipophilic UVB sunscreens, but the UVA sunscreen 2-hydroxy-4-methoxy benzophenone (commonly known as benzophenone-3 or oxybenzone), which has an absorption spectrum of 270–350 nm, is known to be systemically absorbed following administration to the skin [4–6]. For example, topical absorption leading to excretion of oxybenzone and its metabolites in the urine [4–6] and breast milk [7] has been reported.

Various strategies to reduce the systemic uptake of drugs by targeting the molecules to the upper layers of the skin have been investigated. Jiang *et al.* studied the influence of a range of vehicles on the diffusion of oxybenzone into and across polyethylene membrane and human epidermis [8]. They reported that the flux and permeability coefficient of oxybenzone is related to

* Author for correspondence. E-mail: h.benson@curtin.edu.au

vehicle solubility parameter [8]. Increased solubility of oxybenzone in the vehicle reduced the thermodynamic activity of the solute in the vehicle, thereby decreasing solute availability from the vehicle, leading to reduced permeability. Walters *et al.* also demonstrated the influence of vehicle on skin penetration of the highly lipophilic sunscreen octyl salicylate [9]. Due to the poor water solubility of many sunscreen chemicals, vehicles for sunscreen products tend to include oils or alcohols to facilitate formulation. In some cases, these vehicles may interact with the stratum corneum barrier to act as skin penetration enhancers [10]. Thus, enhanced sunscreen solubility with minimal use of organic solvent would be advantageous.

The current study investigates the use of cyclodextrins to facilitate aqueous solubility of sunscreens and minimize release from the vehicle. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α-, β-, γ-cyclodextrin respectively) bound in a 1,4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes [11]. This can result in improved stability and/or increased aqueous solubility and dissolution of poorly water-soluble drugs [12]. β-Cyclodextrin (βCD) has low aqueous solubility (18.5 mg/mL at 25 °C), therefore derivatives with enhanced solubility, such as 2-hydroxypropyl-β-cyclodextrin (HPβCD) and dimetyl-β-cyclodextrin (dimethylβCD), are more commonly used in pharmaceutical formulation.

Cyclodextrins may be useful in topical formulation of lipophilic solutes. First, they could enhance aqueous solubility, thereby facilitating formulation without the need for organic and mixed solvents that may have penetration enhancement properties. Second, the molecular size of the solute–cyclodextrin complex may act to retard skin penetration. A limited number of studies have been published on the use of cyclodextrins in topical formulation. Szente and co-workers reported improved stability, wettability and dissolution of the lipophilic insect repellent *N*,*N*-diethyl-m-toluamide (deet) by formulation of inclusion complexes with βCD [13]. The solubility and photostability of sunscreen chemicals was increased by complexation with HPβCD [14, 15].

There are reports of both increased and decreased skin penetration of drugs due to cyclodextrin complexation. For example, penetration of lirazole across rat skin was increased by complexation with HPβCD and dimethylβCD [16]. Based on thermal analysis data, the authors suggested that dimethylβCD interacts with proteins and disorders the stratum corneum bilayer lipid structure. Similar changes were not observed with HPβCD. Recently, the ability of HPβCD and γCD to reduce the release of deet from vehicles was demonstrated [17]. Williams and co-workers demonstrated the use of cyclodextrins to reduce skin penetration of estradiol and toluene [18]. The effect on skin penetration

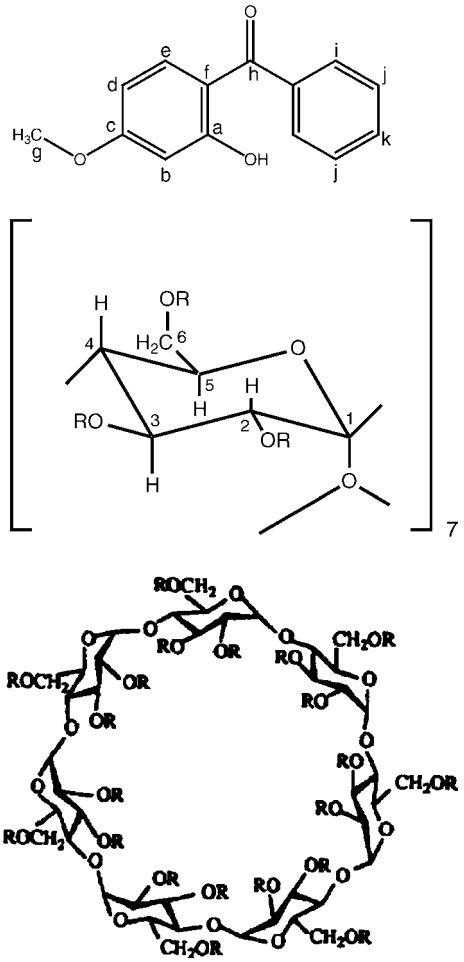

Figure 1. The chemical structures of 2-hydroxy-4-methoxy-benzophenone or oxybenzone (upper) and HPβCD. R = —$CH_2CH(OH)CH_3$ or –H, with average molar substitution of 0.75.

may be related to CD concentration. In a recent review of the literature, Loftsson *et al.* concluded that reduced permeability is generally observed at relatively high concentrations of cyclodextrins [19].

The aim of the present study was to prepare and assess a complex between oxybenzone and HPβCD (Figure 1). This complex was characterized by phase solubility studies, nuclear magnetic resonance (NMR) spectroscopy and thermal analysis. The effect of complexation on the UV transmittance spectra of oxybenzone (as a measure of sunscreen efficacy) and its diffusion across a synthetic membrane was assessed.

Experimental

Materials

Oxybenzone was purchased from Aldrich (USA). β-Cyclodextrin (βCD) and hydroxypropyl-β-cyclodextrin (HPβCD) (molar substitution 0.6–0.9) were generously provided as gifts by Wacker Biochem Corporation (USA). Bovine serum albumin (BSA) was from Sigma

(USA). Methanol and acetonitrile were high-performance liquid chromatography (HPLC)-grade from Fisher Scientific (USA). Deionized water was used and all other chemicals were analytical-reagent grade.

Determination of oxybenzone solubility

A moderate excess of oxybenzone was placed in 10 mL of each solvent (30, 45 and 60% aqueous ethanol) and stirred in the dark at 25 ± 0.1 °C for 72 h. Each mixture was then centrifuged at 10,000 × *g* for 10 min. This step was repeated with the resulting supernatant, prior to analysis of oxybenzone concentration by HPLC.

Phase solubility studies

Solubility measurements were performed according to the method of Higuchi and Connors [20]. An excess amount of oxybenzone was added to aqueous solutions containing different concentrations of the cyclodextrins (0–15 mM for βCD and 0–60 mM for HPβCD). The suspensions were stirred in 10 mL screw-capped vials at 25 ± 0.1 °C and shielded from light. After equilibration for 72 h (previously validated), the contents of each vial were filtered through a 0.45 μm membrane filter (Millipore, USA) and analyzed by HPLC to determine the concentration of oxybenzone.

Preparation of the inclusion complex

The inclusion complex was prepared at an equimolar ratio of oxybenzone to HPβCD as reported below. Oxybenzone (114.1 mg, 0.5 mmol) dissolved at room temperature in 95% ethanol (10 mL) was added to purified water (10 mL) containing HPβCD (700 mg, 0.5 mmol). The resulting solution was stirred for 24 h at room temperature and shielded from light. The solvent was evaporated under vacuum at 40 °C by rotary evaporation. The solid complex was dried under vacuum in a desiccator for 3 days with phosphorus pentoxide as a drying agent. The oxybenzone content of the complex was determined by HPLC.

Thermal analysis

Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were performed on a Metler TGA/SDTA 851 and Metler DSC/821 respectively. Samples of oxybenzone, HPβCD and the complex were scanned at a heating rate of 20 °C per min under a flow of nitrogen (50 mL/min).

NMR spectroscopy

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively using a Bruker Avance 300 spectrometer (Karlsruhe, Germany). Samples were dissolved in deuteromethanol, and chemical shifts (δ) for hydrogen and carbon resonance were reported in ppm relative to TMS.

High-performance liquid chromatography

An Alliance liquid chromatographic system (Waters Inc., USA) equipped with a 2690 Separations Module and 996 Photodiode Array detector, was used. Separation was achieved on a Symmetry C_{18} column (5 μm, 3.9 × 150 mm I.D., Waters Inc., USA) at ambient temperature, with an inline pre-filter. Integration was undertaken using a personal computer equipped with Millenium version 4.0 software.

The mobile phase consisted of methanol:water [85:15], filtered through a 0.45 μm membrane filter (Durapore membrane filter, Millipore, USA). The mobile phase was continuously degassed before and during use. The flow rate was 1.0 mL/min and the detection wavelength set at 289 nm. The retention time for oxybenzone was ~2.4 min. Calibration curves were calculated on peak area measurements and the assay was fully validated. Extraction of oxybenzone from 4% BSA solutions was achieved using solvent precipitation of proteins. Briefly, 100 μL sample of oxybenzone in BSA solution was mixed with 200 μL acetonitrile:methanol (95:5), refrigerated at 4 °C for 15 min, then centrifuged at 10,000 × *g* for 10 min to precipitate proteins prior to HPLC analysis. This extraction was validated with a recovery of 99.6 ± 1.08% from BSA solutions.

UV Transmittance spectral analysis

Solutions for UV spectral analysis were prepared in ethanol using oxybenzone alone and in combination with cyclodextrin. The method for determining transmittance has been reported previously [21, 22]. Four combinations were prepared in 100 mL of ethanol containing (i) 1 mg oxybenzone (4.38×10^{-3} mmol), (ii) 1 mg oxybenzone and 12.6 mg HPβCD (8.75×10^{-3} mmol), (iii) 1 mg oxybenzone and 6.3 mg HPβCD (4.38×10^{-3} mmol), (iv) 1 mg oxybenzone and 3.15 mg HPβCD (2.19×10^{-3} mmol). UV transmittance curves of each solution were obtained with the aid of a UV/VIS spectrophotometer with scanning wavelengths between 290 and 400 nm (Shimadzu, Japan). A background correction was performed using 1cm quartz cells filled with blank solvent. The UVA transmittance was determined as the area under the transmittance curve in the 320–400 nm region for each solution divided by the area under the transmittance spectrum for these wavelengths in the absence of sunscreen and/or HPβCD, and then multiplied by 100.

In vitro release and membrane diffusion

Oxybenzone release and membrane permeation was determined across a synthetic model membrane

(polydimethyl siloxane, PDMS). *In vitro* permeation studies across PDMS were performed in Franz-type diffusion cells (cross sectional surface area 1.18 cm^2). The membrane was immersed in deionized water for 1 h, then mounted between the donor and receptor compartments of diffusion cells and the assembly held in place with a plastic clamp. The receptor chamber (approx. 3.5 mL) was filled with 4% BSA in phosphate buffer (pH 7.4), stirred continuously in a water bath at 37 ± 0.1 °C. The donor phase consisted of 1 mL of each of the test formulations of oxybenzone, i.e., saturated solutions of oxybenzone in 30, 45 and 60% aqueous ethanol; saturated solutions of oxybenzone in 45 and 60% ethanol containing equimolar or 2 times molar concentrations of HPβCD; and saturated solutions in 30% ethanol with 1, 2 and 4% HPβCD. Aliquots of 100 μL of the receptor fluid were withdrawn for HPLC analysis and replaced periodically for 6 h. Experiments were conducted in triplicate.

The flux of oxybenzone through the membranes into the receptor fluid from each of the formulations was determined from slopes of plots of cumulative concentration in the receptor phase *versus* time and expressed as $\mu g\ cm^{-2}\ h^{-1}$. Permeability coefficients were calculated for oxybenzone from each formulation. The difference between the cumulative amount of oxybenzone in the receptor *versus* time plots was assessed using multiple regression with pair-wise comparison. One-way ANOVA followed by Bonferroni's comparison test was used for assessing the decrease in permeability coefficient of oxybenzone with increased concentration of ethanol and on addition of HPβCD. The level of significance was set at $p < 0.05$.

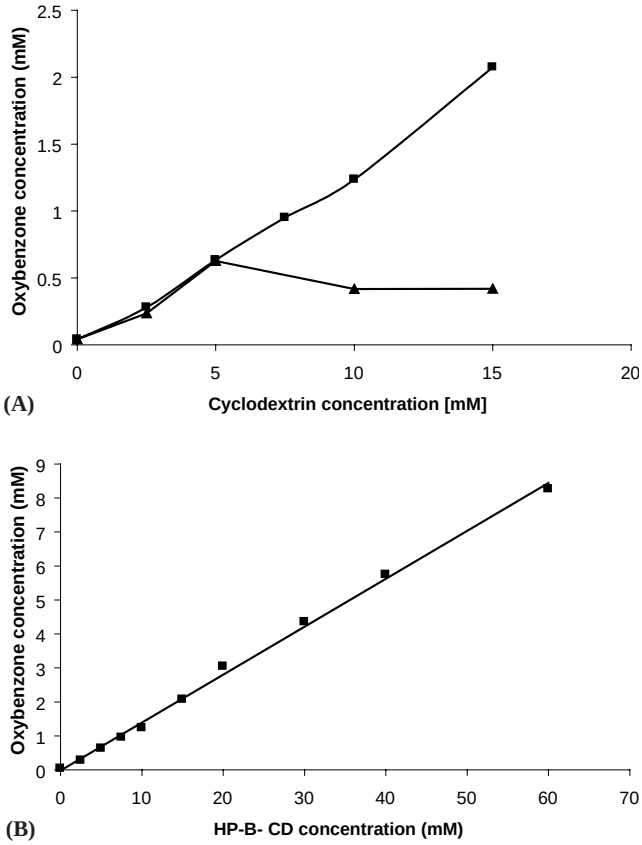

Figure 2. (A) Phase solubility diagrams in water at 25 °C for oxybenzone with (0–15 mM) (▲, βCD and ■, HPβCD). (B) Phase solubility diagram in water at 25 °C for oxybenzone in the presence of HPβCD (0–60 mM).

Results and discussion

Characterization of the complex

The phase solubility studies of oxybenzone in aqueous solutions of different concentrations of βCD and HPβCD examined are shown in Figure 2A. Of the two cyclodextrins used, only HPβCD caused a substantial increase in aqueous solubility of oxybenzone, and consequently, only HPβCD was selected for further experiments. The slope of the solubility curve (Figure 2B) is less than unity and the linear A_L-type relationship suggest a 1:1 complex stoichiometry of oxybenzone with HPβCD [20]. The apparent stability constant (K) for the oxybenzone-HPβCD complex was calculated from the slope and intercept values of the initial straight-line portion of the solubility diagram, according to the following equation:

$$K_{1:1} = \text{slope}/(\text{intercept}\ (1 - \text{slope})$$

We assume that a 1:1 stoichiometric complex exists in the solution and that the linear region has a slope less than unity, a condition that does exist. The apparent stability constant (K) for the oxybenzone-HPβCD complex was calculated to be 5839 M^{-1}.

The complex was characterized in the solid state by thermal analysis using DSC and TGA. DSC curves for HPβCD showed a shallow endotherm at 110 °C. A sharp melting point endotherm was observed for oxybenzone at 67 °C. A slight deviation in this sharp melting point endotherm for oxybenzone was observed in the presence of HPβCD (65 °C), and the shallow endotherm for HPβCD was shifted from 110 to 117 °C in the presence of oxybenzone. These deviations indicate an interaction between oxybenzone and HPβCD. Recently, Felton *et al.* [23] also demonstrated the complexation between oxybenzone and HPβCD using differential scanning calorimetry. Further confirmation was provided by the TGA curve of the oxybenzone-HPβCD complex that shows that the interaction of oxybenzone with HPβCD leads to a dramatic reduction in weight loss of oxybenzone, when compared to oxybenzone alone (Figure 3). The weight loss at the inflect point for oxybenzone (185.11 °C) and HPβCD (352.12 °C) alone were 99.18 and 86.79% respectively. The complex has two inflect points with a weight loss of only 5.44% at 179.62 °C and a major weight loss of 74.21% at 328.23 °C. These

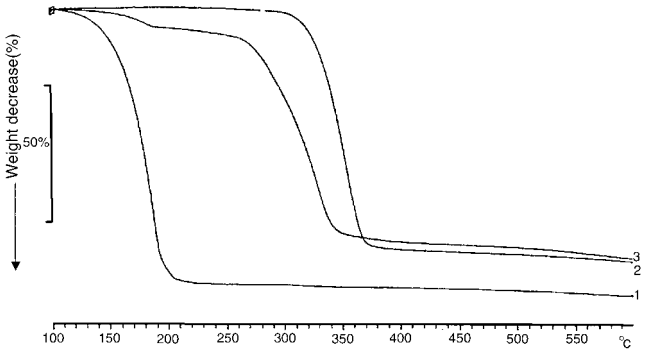

Figure 3. TGA thermograms for (1) oxybenzone, (2) HPβCD, (3) oxybenzone – HPβCD complex.

changes can be ascribed to interaction of oxybenzone with HPβCD. Hence, the results of thermal analysis indicate an interaction between the two moieties. Benzophenone, the parent molecule of benzophenone-3 or oxybenzone has been demonstrated to form a stable inclusion complex with cyclodextrins. βCD possessed the best complexing ability with benzophenone when compared with α- and γ-CD [24].

NMR studies were performed to obtain further evidence to determine the interaction between the sunscreen molecule and the cyclodextrin moiety in deuteromethanol. The ^{1}H NMR shifts (Table 1) of the HPβCD alone or as a complex with oxybenzone demonstrate that the presence of the sunscreen molecule induces changes in the chemical shift values for the proton (H-5) located inside the cyclodextrin cavity and the external protons. This implies interaction of the guest molecule with the external surface of the cyclodextrin. Comparison of the ^{13}C NMR spectrum of cyclodextrin alone and in the presence of oxybenzone shows significant upfield chemical shifts in carbons 3 and 5 in the ring (Table 1; see Figure 1). The data obtained indicate that the ^{13}C chemical shifts are more sensitive to complexation than the ^{1}H shifts. These shifts are indicative of an interaction between the oxybenzone and cyclodextrin molecule.

Table 2 reports some of the ^{1}H and ^{13}C chemical shifts of oxybenzone in the free form and in the presence of HPβCD. As observed for cyclodextrin, the ^{13}C signals are more affected than those from ^{1}H. Interaction with HPβCD produces shifts in protons on oxybenzone, large shifts being observed in protons on carbon b, d, e, g, and k. These data are indicative of strong interaction of oxybenzone with the HPβCD, and are confirmed by large ^{13}C chemical shifts. Comparison of the ^{13}C NMR spectrum of oxybenzone in the absence and presence of cyclodextrin shows significant downfield chemical shifts in the carbons b, d, e, and the methoxy carbon (g) of oxybenzone (Table 2). This is in agreement with the deshielding phenomenon previously reported [25], in which the carbons interacting with the external part of the cavity are shifted downfield. Moreover, the negative shift on the aromatic carbon k suggests an insertion of this part of the molecule into the cyclodextrin cavity [26]. Therefore, the NMR results strongly indicate complexation of oxybenzone with HPβCD.

Ultra-violet transmittance studies

Measured sun protection factors (SPF) provide a measure of the time of skin exposure to sunlight required to induce erythema in the presence of a sunscreen as compared to no protection. Theoretical SPFs calculated from UV transmittance spectra have been reported to show correlation with the actual measured SPF values [20]. This study measures the UV transmittance spectra of oxybenzone, as a preliminary measure for SPF and the effect of complexation with HPβCD (Figure 4). Since oxybenzone is primarily considered as a UVA sunscreen agent, percent UVA transmittance was also calculated. The UVA transmittance was determined from the area under the transmittance curve in the 320–400 nm region for each solution (A, B, C, and D) divided by the area under the transmittance spectrum for these wavelengths in the absence of sunscreen and/or HPβCD (Figure 4). The percent transmittance decreased with an increase in the concentration of HPβCD: percent UVA transmittance was 74.76, 74.05, 68.94, and 66.11 for solution A, B, C, and D, respectively. The results suggest that HPβCD complexation does not decrease the UVA absorbing properties of oxybenzone, and that a sunscreen formulation incorporating the

Table 1. ^{1}H and ^{13}C NMR chemical shifts (δ, ppm) for HPβCD in the absence and presence of oxybenzone

	1	2	3	4	5	Methyl
^{1}H NMR chemical shift, δ, for the proton on carbon no.:						
HPβCD	5.003	3.733	3.973	3.525	3.849	1.15
Oxybenzone-HPβCD complex	4.995	3.731	3.972	3.515	3.838	1.145
$\Delta\delta$	−0.008	−0.002	−0.001	−0.01	−0.011	−0.005
^{13}C NMR chemical shift, δ, for carbon no.:						
HPβCD	102.051	74.944	83.472	74.088	62.294	19.525
Oxybenzone-HPβCD complex	102.012	74.933	83.344	74.071	62.062	19.594
$\Delta\delta$	−0.039	−0.011	−0.128	−0.017	−0.232	0.069

Table 2. ^{1}H and ^{13}C NMR chemical shifts (δ, ppm) for oxybenzone in the absence and presence of HPβCD

	b	d	e	g	i	j	k
^{1}H NMR chemical shift, δ, for the proton on carbon:							
Oxybenzone	6.449	6.478	6.528	3.858	7.58	7.63	7.606
Oxybenzone- HPβCD complex	6.505	6.535	6.561	3.893	7.61	7.665	7.641
$\Delta\delta$	0.056	0.057	0.033	0.035	0.03	0.035	0.035

^{13}C NMR chemical shift, δ, for carbon:	b	c	d	e	f	g	h	i	j	k
Oxybenzone	102.339	168.061	108.313	132.796	114.446	56.365	201.68	129.987	129.552	136.605
Oxybenzone- HPβCD complex	102.449	168.086	108.451	132.911	114.433	56.52	201.708	130.012	129.682	136.54
$\Delta\delta$	0.11	0.025	0.138	0.115	−0.013	0.155	0.028	0.025	0.13	−0.065

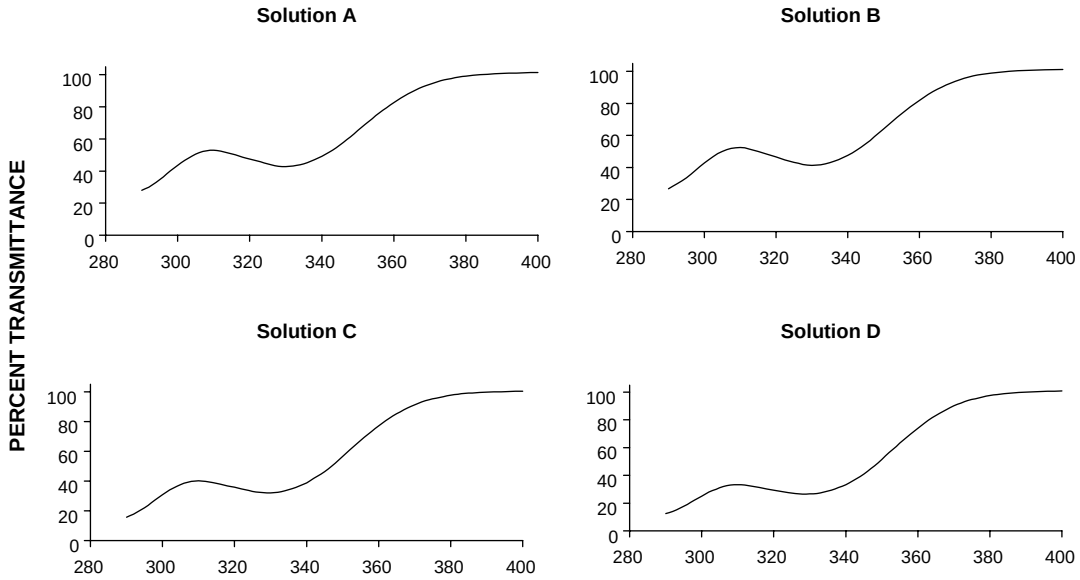

Figure 4. Transmittance Spectra of (A) 1 mg oxybenzone (4.38×10^{-3} mmol); (B) 1 mg oxybenzone and 12.6 mg HPβCD (8.75×10^{-3} mmol); (C) 1 mg oxybenzone and 6.3 mg HPβCD (4.38×10^{-3} mmol); (D) 1 mg oxybenzone and 3.15 mg HPβCD (2.19×10^{-3} mmol) in ethanol.

HPβCD complex would be as effective as oxybenzone alone.

In vitro release and membrane diffusion

The release study was designed to determine if increased affinity of oxybenzone towards the vehicle would result in a decrease in release rate and thereby decrease penetration. Since the solubility of oxybenzone increases with an increase in the percentage of ethanol (0.134 ± 0.005 mg/mL, 1.43 ± 0.06 mg/mL, and 6.39 ± 0.17 mg/mL in 30, 45, and 60% ethanol, respectively), the thermodynamic activity of the drug is expected to decrease in the same order and thereby result in decreased release from the vehicle. Permeability coefficient K_p, values are often used to compare penetration profiles of solutes examined under different conditions and relate to the rate of diffusion of a solute within a membrane adjusted for differences in concentration. As expected, the permeability coefficient of oxybenzone decreased significantly with increase in the percentage of ethanol from 30 to 60% (Figure 5).

Further studies were designed to evaluate whether HPβCD is capable of increasing the affinity of oxybenzone towards the vehicle, which would result in decreased thermodynamic activity of the solute in the vehicle. This would decrease the release of solute from the vehicle, and thereby, reduce permeability. Equimolar and 2 times molar concentration of HPβCD decreased the release of oxybenzone from the vehicle containing 45 and 60% ethanol when compared to oxybenzone alone. This is reflected by lower values of permeability coefficient ($p < 0.01$) as shown in Figure 5. Oxybenzone release was also reduced in the 30% ethanol vehicle when an excess of HPβCD (1%) was added (Figure 6) ($p < 0.01$). Further, decrease in release was seen with increase in the concentration of HPβCD to 2 and 4% ($p < 0.01$).

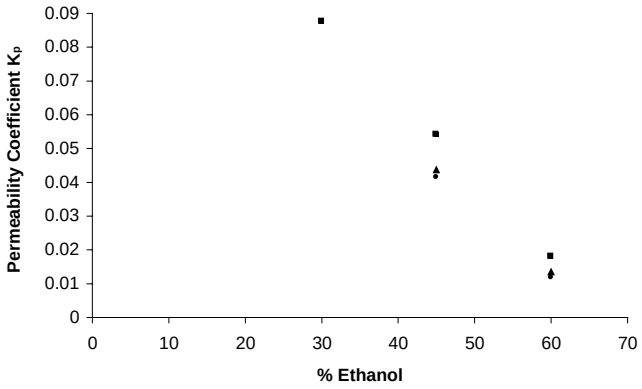

Figure 5. Effect of ethanol (■) and HPβCD (▲, equimolar; ●, 2 times molar) on permeability of oxybenzone through PDMS membrane.

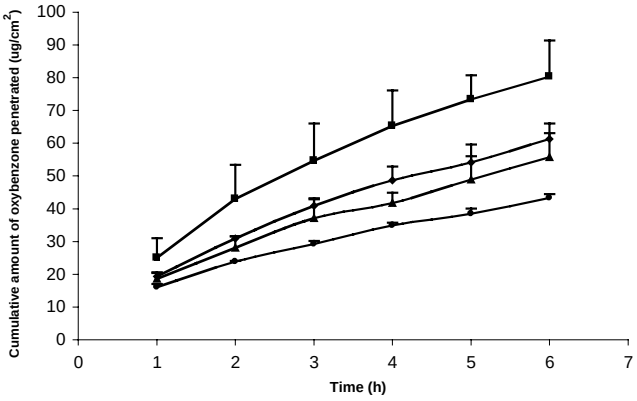

Figure 6. Penetration profiles of oxybenzone across PDMS membrane. Data represents mean ± sd of three replicates. The donor phase was saturated solution of oxybenzone in 30% ethanol (■), with 1% (♦); 2% (▲); 4% HPβCD (•).

Conclusions

Complexation of oxybenzone with HPβCD was demonstrated in the solid state by thermal analysis (DSC and TGA) and in solution by phase solubility and NMR spectroscopic studies. It is concluded that HPβCD can reduce the release and membrane diffusion of oxybenzone whilst retaining its efficacy as a sunscreen agent. This formulation strategy may be useful in controlling skin penetration of sunscreens and other topically applied chemicals. It is possible that inclusion of oxybenzone in HPβCD may also be beneficial in limiting interaction of UV filter with the skin and thus reducing irritation and allergic side effects. Further studies on human epidermis are currently being undertaken. In addition, the influence of cyclodextrin complexation on oxybenzone oxidation [27] and formation of toxic photoproducts following UVR exposure should be investigated, as this may be a further advantage.

Acknowledgements

The authors wish to acknowledge the financial support of the Canada Foundation for Innovation and the Manitoba Infrastructure Fund. VS acknowledges the support of a University of Manitoba Graduate Fellowship and a Leslie F. Buggey Graduate Fellowship. We also thank Dr Alaa S. Abd-El-Aziz (University of Winnipeg) for thermal analysis, Dr Kirk Marat, Department of Chemistry (UM) for NMR analysis, Subuddhi Kulkarni for useful discussions, Wacker Biochem Corp. for supply of cyclodextrins, and Dr Frank Burczynski (UM) for his input.

References

1. US National Cancer Institute, Sunscreens. Class study report; Contract No. NOI-CP-71082 (7/89), Tracor Technological Resources Inc, Rockville MD, 1989.
2. J. Knowland, E.A. McKenzie, P.J. McHugh, and N.A. Cridland: *FEBS Lett*. **324**(3), 309 (1993).
3. C. Xu and P.G. Parsons: *Photochem. Photobiol*. **69**(5), 611 (1999).
4. C.G. Hayden, M.S. Roberts, and H.A.E. Benson: *Lancet* **350**(9081), 863 (1997).
5. V. Sarveiya, S. Risk, and H.A.E. Benson: *J. Chromatogr. B*., **803**, 225 (2004).
6. H.A. Benson: *Am. J. Clin. Dermatol*. **1**(4), 217 (2000).
7. J. Hany and R. Nagel: *Deutsche Lebensmittel-Rundschau* **91**, 341 (1995).
8. R. Jiang, H.A.E. Benson, S.E. Cross, and M.S. Roberts: *Pharm. Res*. **15**(12), 1863 (1998).
9. K.A. Walters, K.R. Brain, D. Howes, V.J. James, A.L. Kraus, N.M. Teetsel, M. Toulon, A.C. Watkinson, and S.D. Gettings: *Food Chem. Toxicol*. **35**(12), 1219 (1997).
10. A. Williams and B. Barry: *Crit. Rev. Ther. Drug Carrier Syst*. **9**(3–4), 305 (1992).
11. T. Loftsson and M.E. Brewster: *J. Pharm. Sci*. **85**(10), 1017 (1996).
12. R.A. Rajewski and V.J. Stella: *J. Pharm. Sci*. **85**(11), 1142 (1996).
13. L. Szente, H. Magisztrak, and J. Szejtli: *Pestic. Sci*. **28**, 7 (1990).
14. S. Scalia, S. Villiani, A. Scatturin, M.A. Vandelli, and F. Forni: *Int. J. Pharm*. **175**, 205 (1998).
15. S. Scalia, S. Villani, and A. Casolari: *J. Pharm. Pharmacol*. **51**(12), 1367 (1999).
16. U. Vollmer, B.W. Muller, J. Peeters, J. Mesens, B. Wilffert, and T. Peters: *J. Pharm. Pharmacol*. **46**(1), 19 (1994).
17. S. Proniuk, B.M. Liederer, S.E. Dixon, J.A. Rein, M.A. Kallen, and J. Blanchard: *J. Pharm. Sci*. **91**(1), 101 (2002).
18. A.C. Williams, S.R. Shatri, and B.W. Barry: *Pharm. Dev. Technol*. **3**(3), 283 (1998).
19. T. Loftsson and M. Masson: *Int. J. Pharm*. **225**(1–2), 15 (2001).
20. T. Higuchi and K.A. Connors: *Adv. Anal. Chem. Inst*. **4**, 117 (1965).
21. B.S. Rosenstein, M.A. Weinstock, and R. Habib: *Photodermatol. Photoimmunol. Photomed*. **15**(2), 75 (1999).
22. L.E. Agrapidis-Paloympis, R.A. Nash, and N.A. Shaath: *J. Soc. Cosmet. Chem*. **38** (July/August), 209 (1987).
23. L.A. Felton, C.J. Wiley, and D.A. Godwin: *Drug Dev. Ind. Pharm*. **28**(9), 1117 (2002).
24. S. Monti, L. Flamigni, A. Martelli, and P. Bortolus: *J. Phys. Chem*. **92**, 4447 (1988).
25. Y. Inoue, H. Hoshi, M. Sakurai, and R. Chujo: *J. Am. Chem. Soc*. **107**, 2319 (1985).
26. M.A. Vandelli, G. Salvioli, A. Mucci, R. Panini, L. Malmusi, and F. Forni: *Int. J. Pharm*. **118**, 77 (1995).
27. K.U. Schallreuter, J.M. Wood, D.W. Farwell, J. Moore, and H.G. Edwards: *J. Invest. Dermatol*. **106**(3), 583 (1996).