Percutaneous Absorption of Sunscreens Through Micro-Yucatan Pig Skin *In Vitro*

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Purpose. The objectives of this study were to develop an in vitro model for studying sunscreen permeation in skin, and evaluate the influence of formulation differences.

Methods. The sunscreens studied were two of the most widely used agents, octyl methoxycinnamate (OMC) and benzophenone-3. Preparations containing radiolabeled actives were applied to micro-Yucatan pig skin dermatomed to a thickness of 250–300 μm as a finite dose in a flow-through diffusion system. At the end of each experiment the amounts removed by washing, retained inside stratum corneum (SC) and penetrated into receptor and viable skin were determined.

Results. The two sunscreens reached a peak level in SC within an hour. Benzophenone-3 penetrated skin to a greater extent than OMC. The opposite was true when comparisons of SC retention were made. The ratio of retained to penetrated amount of sunscreens from a hydroalcoholic formulation at the end of 10 hours was higher when the sunscreens were present together than alone.

Conclusions. Despite the highly lipophilic nature of sunscreens, particularly OMC, SC is the rate limiting skin layer for penetration. Penetration and SC retention were formulation dependent. The ratio of SC content to the amount penetrated is a useful tool for evaluating sunscreen permeation.

KEY WORDS: in vitro percutaneous absorption; octyl methoxycinnamate; benzophenone-3; sunscreens; retention inside stratum corneum.

INTRODUCTION

Application of sunscreens is recommended as a means of protecting the skin against ultraviolet radiation and preventing skin cancer. Skin permeation of these agents is of interest because of their frequent administration to large areas of the body under a variety of conditions. Commercial products usually contain a mixture of sunscreens to increase the sun protection factor and intercept a broad spectrum of UV radiation.

Several attempts have been made to quantify the amount of UV-absorbing chemicals which enter the body via the skin (1). The vehicle's nature may modify properties of the SC (e.g., increased hydration) which could influence the penetration profile of active ingredients (2). Hayden *et al.* (3), using an application density six times higher than that for routine SPF measurement (2 mg/cm^2), found that systemic benzophenone-3 absorption over a 10 hour period represented between 1 and 2% of the applied dose. Percutaneous penetration (into the receptor) of octyl salicylate through excised human skin over a 48-hour period was less than 1% of the applied dose (4).

Several researchers have investigated the effect of formulation on sunscreen permeation through the skin. The absorption of OMC and benzophenone-3 was studied in human subjects using a skin stripping technique (5). The SC contained much higher concentrations than the other skin layers. In an in vitro study utilizing human skin dermatomed to a thickness of 500 μm, various o/w and w/o emulsions yielded almost identical amounts of OMC in the dermis. However, SC deposition from the o/w emulsion was three-fold that from a w/o emulsion (6). Treffel and Gabard (7) used both in vitro and in vivo methods to study the skin penetration of three sunscreens from two vehicles, an o/w emulsion-gel and petroleum jelly. Penetration through the SC was greater with the petroleum jelly formulation while SC retention was lower with this vehicle. The inclusion of 25% adipic acid/diethylene glycol/glycerin (ADG) crosspolymer in sunscreen solutions resulted in reduction of penetration into the viable skin of OMC and benzophenone-3, based on skin stripping experiments with human subjects (8).

The permeability of pig and miniature pig skin have been widely studied and proven to be good animal models for human skin. The skin permeability of nicorandil through human skin was most closely approached using pig skin (9). Pig and human skin have similar surface lipids, barrier thickness and morphological aspects and thus the authors suggested that using excised pig skin would be useful for estimation of in vitro human skin permeation behavior. In vitro permeation rates of nitroglycerin through Yucatan pig and human skin were comparable (10,11).

An objective of this study was to develop an in vitro micro-Yucatan pig skin model for studying sunscreen permeation and to compare results with previously published data utilizing human skin. While human skin is the most relevant for such studies, it is not always readily available and may exhibit considerable site and individual variability. Pig skin is widely accepted as being similar to human skin in its permeation properties and is likely to be more consistent (12).

The influence of two prototypic formulations on permeation of two of the most frequently used sunscreens, benzophenone-3 and OMC was evaluated. Lastly, we wanted to determine whether the sunscreens exhibited the same permeation behavior in combination as in preparations containing only one of them.

MATERIALS AND METHODS

Chemicals and Other Materials

Freshly harvested excised micro-Yucatan pig skin was purchased from Charles River Laboratories, Wilmington, MA. Benzophenone-3, diisopropyl adipate and OMC were obtained from ISP, Wayne, NJ. Physical properties of the sunscreens are summarized in Table I. Radiolabeled sunscreens, [^{14}C] benzophenone-3 with a specific activity of 30.5 mCi/mmol and [^{3}H] OMC (573 mCi/mmol) were obtained from Chemsyn Science Laboratories, Lenexa, KS. Poloxamine 704 (BASF Corp, Parsippany, NJ), SD alcohol 40 (Eastman Chemical Co., Kingsport, TE) and PEG-20 oleyl ether (Croda Inc., Parsippany, NJ) were obtained as research samples. Scintillation fluid, HPLC grade acetonitrile, reagent alcohol, and glacial acetic acid were purchased from Fisher Scientific, Fair Lawn, NJ. Tissue solubilizing fluid (Solvable™), was purchased from Packard Instrument

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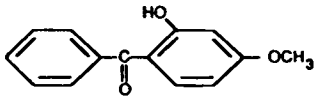
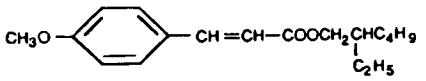
Table I. Physico-Chemical Properties of Benzophenone-3 and OMC

Property	Benzophenone-3	OMC
Chemical name	2-hydroxy-4-methoxybenzophenone	2-ethylhexyl p-methoxycinnamate
Molecular formula	$C_{14}H_{12}O_3$	$C_{18}H_{26}O_3$
Molecular weight	228.3	290.4
*Aqueous solubility	10.24 μg/ml	below limit of detection
log k_{oct} (13)	2.63	5.65
Structure		

* Determined using HPLC method.

Co., Meriden, CT. Transparent tape #800 (Solvable™), was purchased from 3M Packaging Systems Division, St. Paul, MN. All other materials were obtained from standard sources.

Sunscreen Formulations

Percutaneous absorption studies were performed using two model formulations of sunscreens viz., hydroalcoholic and an oil based vehicle, diisopropyl adipate. Formulations contained either a single sunscreen or a mixture of the two. Benzophenone-3 and OMC concentrations were 6 and 7.5% (w/w) respectively in the diisopropyl adipate formulation. The composition of hydroalcoholic formulations are given in Table II.

Receptor Fluid

In these studies, the receptor fluid was an aqueous solution of 0.5% polyoxyethylene oleyl ether (PEG-20 oleyl ether), a nonionic surfactant with an HLB of 16. This receptor fluid, though non-physiologic, increases the solubility of sunscreen agents without affecting skin barrier function (6). The receptor was pumped at a rate of 2.5 ml/h. The volume of receptor chamber was measured to be approximately 0.35 ml. The apparent solubilities of OMC and benzophenone-3 in 0.5% PEG-20 oleyl ether at 37°C were measured to be 243 μg/ml and 153 μg/ml respectively. These solubilities were in excess of fifty-fold of the maximum concentration of sunscreens in the receptor solution at a flow rate of 2.5 ml/h thereby assuring maintenance of sink conditions at all times.

Preparation of Skin Membrane

Micro-Yucatan pig skin was used as the biological membrane to study in vitro percutaneous absorption. Upon receipt the freshly excised skin was washed gently with 1% (w/w) aqueous dish washing detergent, rinsed with deionized water and patted dry with a paper towel. A 250–300 μm thick layer of the skin was cut from the surface with a Padgett™ Electrodermatome instrument (Padgett Instrument, Kansas City, MO). The skin pieces were then rinsed and dried with paper towels before storing them in plastic bags at 4°C. Skin was removed from the refrigerator and kept in isotonic solution to hydrate at room temperature one hour before starting the experiment. The dermatomed skin was then cut into 10 mm circular pieces with a brass punch and placed epidermis-side up in the diffusion cells. The skin treated in this fashion from the stage of receipt until use retained their original permeability characteristics for four weeks after dermatoming (12).

After mounting skin in diffusion cells the receptor fluid was permitted to flow for 15 minutes followed by application of 0.5 ml of deionized water to the skin surface for 30 minutes. After ensuring that the skin was intact (no leakage or drainage), the water was drained out and skin surface patted dry with the tissue paper before the application of sunscreens preparation.

Table II. Composition of Hydroalcoholic Model Formulations

Ingredient	Concentration (% w/w)		
Benzophenone-3	3	3	—
Octyl methoxycinnamate	7	—	7
SD Alcohol 40 (anhydrous)	68	74	71
Poloxamine 704	10	10	10
Water	12	13	12

Radiolabeling of Sunscreen Formulations

[^{14}C] benzophenone-3 was obtained as solid material and was solubilized in ethanol to give a specific activity of 1.05 μCi/μl of solution. Sunscreen preparations were spiked with the radiolabeled solution so that each μg of benzophenone-3 applied on the skin surface had approximately 1600 dpm (disintegrations per minute) for the hydroalcoholic preparations, and 600 dpm for the diisopropyl adipate oil formulations. [^{3}H] OMC was obtained as solution in toluene with a specific activity of 1.93 μCi/μl. Sunscreen preparations were spiked with the radiolabeled solution so that each μg of OMC applied on the skin surface for permeation studies had 1600 dpm for hydroalcoholic preparations, and 450 dpm for diisopropyl adipate formulations.

Dosing

Finite dosing was used to simulate the actual use conditions in all of the in vitro skin permeation experiments. The smallest volume of sunscreen preparation required to obtain complete and uniform coverage of the diffusion cell surface area (approx. 0.636 cm^2) was determined to be 4 μl corresponding to a weight

of between 3 and 4 mg. After application the preparation was uniformly spread on the SC side of the skin with the help of a glass rod and the tip of the rod was washed into a vial containing 2 ml of alcohol in order to account for the material lost in spreading. With this technique the exact amount of material applied on to the skin surface was obtained.

In Vitro Skin Permeation Methodology

A flow-through system was used for conducting in vitro permeation experiments. The total system consisted of a receptor fluid reservoir, a variable flow rate peristaltic pump, Cassette™ (Manostat, New York, NY), a circulating water bath, Lauda™ (Brickman instrument, Westbury, NY), 2 cell-holding heating blocks, 14 Teflon™ flow-through diffusion cells, and a Retriever IV fraction collector (ISCO Inc., Lincoln, NE) to collect effluent fractions over the adjusted time period. Each diffusion cell had an inner diameter of 9 mm and a surface area of 0.636 cm^2 exposed to the receptor fluid. The skin surface temperature was maintained at 32°C by adjusting the circulating water bath temperature to 39°C (14). The effluent from diffusion cells were collected directly into polyethylene scintillation vials.

Skin Treatment and Analysis

The liquid scintillation counting technique was used to analyze all the in vitro skin permeation samples. In each experiment a minimum of four replicates were used. At the conclusion of the experiment, usually 10 hours, scintillation fluid was added to the effluent samples collected directly into the vials and amount of sunscreens penetrated was estimated from the counts of radioactivity present in the samples. The donor compartment was washed thrice with 1 ml of a mixture of water/ethanol = 1:1 (6). Washes were then analyzed for the amount of sunscreen remaining on the surface. Washed skin samples were removed from the cells. It was necessary to separate the SC from rest of the epidermis to get an account of material remaining inside the barrier layer of the skin by tape-stripping. In this technique, seventeen strippings of the sunscreen-treated site of the skin using transparent 3M Scotch™ tape were taken on a single piece. For each strip, a fresh tape surface was used. Sunscreens recovered from the 17 strips were considered as the amount inside SC. Scintillation fluid was added to the vials containing tape strips and allowed to stand at room temperature for at least 24 hours to enable extraction of sunscreens in order to perform scintillation counting on the samples.

The remainder of the skin was digested in 2 ml of tissue solubilizer at 50°C for 24 hours in an oven. This was done to get the estimate of material in the viable tissues of the skin. After skin digestion, the samples were neutralized with glacial acetic acid and scintillation fluid was added for scintillation counting. Thus, the amount of sunscreen was estimated in four locations in each in-vitro percutaneous absorption experiment:

(i) the receptor fluid
(ii) the washes
(iii) SC (from the strippings)
(iv) viable tissues of the skin (from the digested skin)

Statistical Analyses

Sigma Stat 2.0 (Jandel Scientific, San Rafael, CA) was used to perform statistical analyses on the data. Whenever analysis of variance on data showed significant differences amongst observations, Dunnett's test was used as it allowed comparisons with the control observation.

RESULTS

Time Dependence of Sunscreens Skin Distribution

In order to quantitate the distribution of sunscreens in various layers of the skin with time, a series of in vitro skin permeation studies terminating at the end of 1, 2, 6, and 10 hours after their initial application were conducted. The formulations contained a combination of both sunscreens. Figure 1 shows that both sunscreens reached a peak value within one hour which remained essentially constant thereafter. These findings agreed well with the results of Treffel and Gabard (7) who noticed maximum levels of benzophenone-3 and OMC inside SC from emulsion-jel and petroleum jelly formulations in in-vivo experiments after 30 minutes of product application. One other important observation they reported was that after removal of the non-penetrated product, the SPF value for the emulsion-gel formulation was reduced to about half of the original value and this corresponded to 50% of the applied dose remaining inside the SC.

Figure 1 also shows that the quantities of OMC were greater than benzophenone-3 inside SC at all time points for both the hydroalcoholic and diisopropyl adipate formulations which was consistent with the observations of Cernasov and

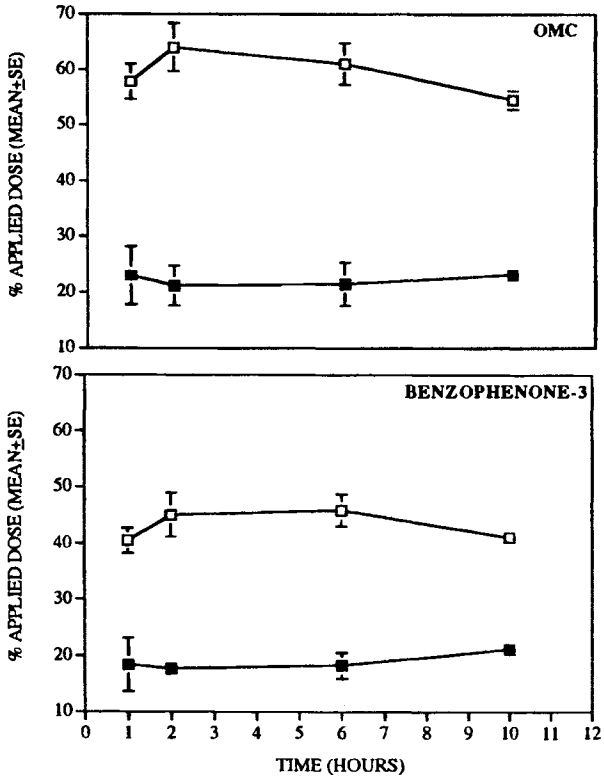


Fig. 1. Retention of sunscreens inside SC of excised micro-Yucatan pig skin. The amounts retained from hydroalcoholic (open squares, n = 5) and diisopropyl adipate (closed squares, n = 4) formulations are expressed as percent of applied dose. Each point represents the mean ± SE.

Macchio (5) and Carpenter *et al.* (8). The quantities of both sunscreens in SC were higher from the hydroalcoholic than the oily formulation.

The amounts penetrated (viable skin plus receptor) increased slowly over time (Fig. 2). Benzophenone-3 quantities were higher than those of OMC. Similar results were obtained by Treffel and Gabard (7). The amounts of both sunscreens penetrated from hydroalcoholic formulations were greater than diisopropyl adipate containing formulations.

In vitro permeation studies of both formulations containing two sunscreens in combination were carried out. It can be noted from Fig. 3 that absorption of both sunscreens was significantly greater through stripped than intact skin. This treatment increased total OMC penetrated about six-and seven-fold from hydroalcoholic and diisopropyl adipate formulations, respectively. Benzophenone-3 penetration increased three- and five-fold from hydroalcoholic and diisopropyl adipate formulations, respectively as a result of SC removal.

Skin Permeation of Single Sunscreens and Their Mixtures

Permeation was measured from systems containing the two sunscreens individually as well as in combination. The data are collected in Table III. The quantity of either sunscreen reaching the receptor within 10 hours was less than 1% of the applied dose, with the exception of benzophenone-3 in the hydroalcoholic vehicle containing only that sunscreen. Over 85% of penetrated molecules (those crossing the SC) were found in the viable skin tissue. In all cases, for comparable formulations, penetration of benzophenone-3 exceeded that of OMC. The opposite was true when comparisons of SC retention were made; OMC quantities in SC exceeded those of benzophenone-3.

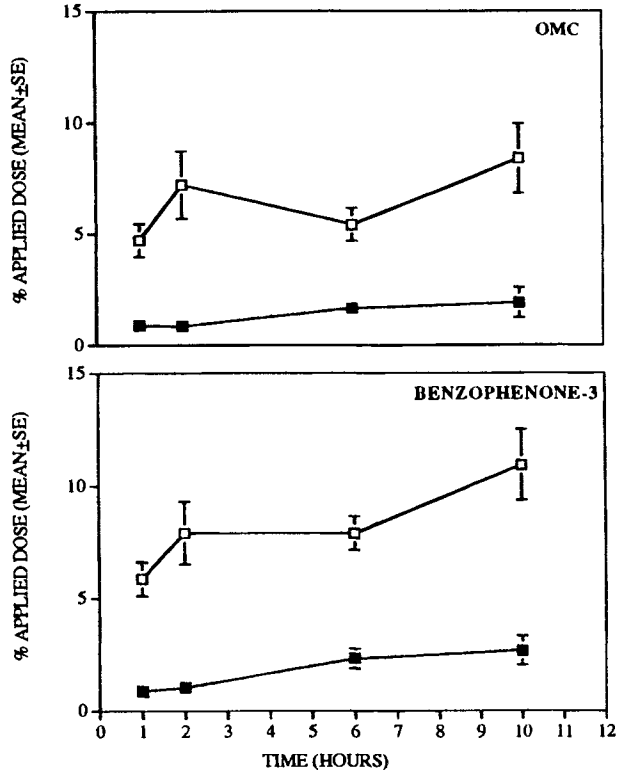


Fig. 2. Total penetration of sunscreens into excised micro-Yucatan pig skin (receptor plus viable skin) following application in hydroalcoholic (open squares, n = 5) and diisopropyl adipate (closed squares, n = 4) formulations are expressed as percent of applied dose. Each point represents the mean ± SE.

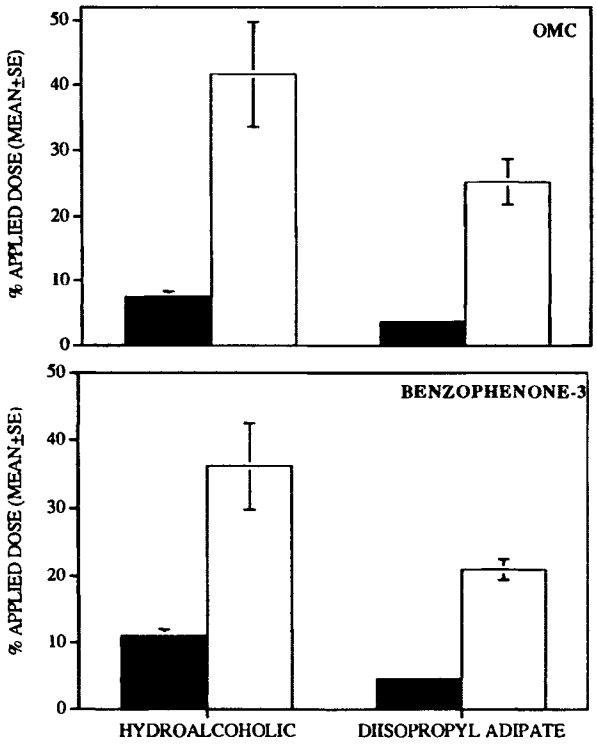


Fig. 3. Total penetration of sunscreens into excised micro-Yucatan pig skin (receptor plus viable skin) following application for 10 hours. Data are expressed as mean percent of applied dose ± SE to stripped skin (open bars, n = 7) and intact skin (solid bars, n = 7 for hydroalcoholic, and n = 12 for diisopropyl adipate formulation).

Benzophenone-3 retention by SC was significantly greater when this sunscreen was present in combination with OMC than with no other sunscreen present. This trend was not observed for OMC. The penetration of OMC was greater when it was alone than in combination, only in the hydroalcoholic vehicle.

Figure 4 depicts the retention to penetration ratio of sunscreens when present alone and in combination in the two formulations. The ratios in hydroalcoholic formulations containing the sunscreens mixture were significantly greater ($p < 0.05$) than when the sunscreens were present alone in the formulation. However, there were no statistically significant differences between the ratios when the sunscreens were present alone and in combination, in the diisopropyl adipate formulations.

DISCUSSION

The greater SC retention of OMC coupled with its decreased penetration may be explained on the basis of the relative partition coefficient values of the two sunscreens. OMC is the more lipophilic sunscreen, with a log octanol-water partition coefficient of 5.65 (compared to a value of 2.63 for benzophenone-3) (13). The higher amounts of benzophenone-3 in receptor fluid agrees with the in vivo percutaneous absorption

Table III. Distribution of Benzophenone-3 and OMC from Hydroalcoholic and Diisopropyl Adipate Model Formulations When Present Individually and in Combination at 10 Hours

	Benzophenone-3		OMC	
Hydroalcoholic	Alone	With OMC	Alone	With benzophenone-3
Receptor	1.81 ± 0.57	0.32 ± 0.01	0.48 ± 0.04	0.36 ± 0.01
Viable skin	12.51 ± 1.30	10.75 ± 0.96	12.56 ± 1.27	7.14 ± 0.85
Penetrated (receptor plus viable skin)	14.32 ± 1.19	11.07 ± 0.96	13.04 ± 1.29**	7.50 ± 0.85**
Retained inside SC	24.26 ± 2.37*	34.00 ± 2.85*	58.13 ± 4.78	55.15 ± 3.82
Diisopropyl adipate				
Receptor	0.33 ± 0.05	0.23 ± 0.01	0.19 ± 0.03	0.19 ± 0.02
Viable skin	2.85 ± 0.44	4.42 ± 0.65	2.55 ± 0.46	3.52 ± 0.40
Penetrated (receptor plus viable skin)	3.18 ± 0.47	4.65 ± 0.65	2.74 ± 0.46	3.71 ± 0.40
Retained inside SC	7.51 ± 1.00*	15.24 ± 1.85*	25.05 ± 3.26	28.21 ± 2.85

Note: All values are % applied dose ± SEM. Combination of sunscreens: n = 12 for diisopropyl adipate, n = 7 for hydroalcoholic formulations. Individual sunscreen formulations, n = 4. Penetrated = receptor + viable skin.
* = $p < 0.05$.
** = $p < 0.01$.

studies in rats published by Okereke *et al.* (15). SC acts as a rate-limiting barrier to penetration of most compounds (16). Increased absorption of sunscreens through stripped skin confirm the importance of the SC as a barrier, even for compounds as lipophilic as these sunscreens. They also provide estimate of the increase in absorption likely to occur in the event that such materials are applied to traumatized skin.

The greater skin uptake and permeation of both sunscreens from the hydroalcoholic vehicle are ascribed to an increase in their activity on the skin surface as a result of solvent evaporation and lower solubility in the vehicle. This should be compared to the persistence of diisopropyl adipate on the skin surface and the affinity of this vehicle for both sunscreens. A skin damaging effect due to the alcoholic vehicle seems unlikely due to the short contact time prior to evaporation.

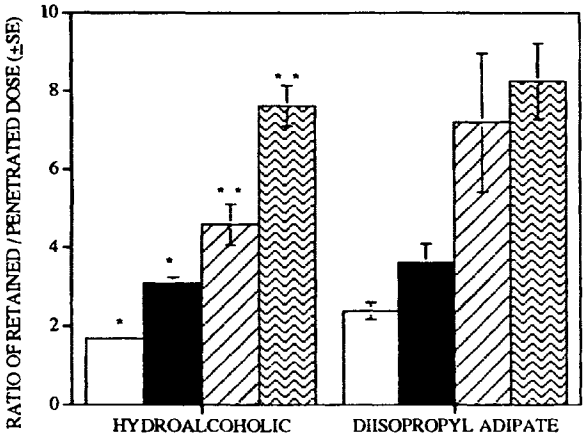


Fig. 4. Ratio of retention to total penetration of sunscreens from hydroalcoholic and diisopropyl adipate formulations. Benzophenone-3 alone (open bars, n = 4), benzophenone-3 in combination with OMC (solid bars, n = 7 for hydroalcoholic, and n = 12 for diisopropyl adipate formulation), OMC alone (hatched bars, n = 4), and OMC in combination with benzophenone-3 (wavy bars, n = 7 for hydroalcoholic, and n = 12 for diisopropyl adipate formulation).

The increase in retention to penetration ratio noted when sunscreens were combined rather than utilized separately, particularly in hydroalcoholic formulations, is of great practical importance. The data were further evaluated, taking into account the intended purpose of sunscreen preparations. To intercept UV radiation, sunscreen molecules must be present either on the skin surface or in the SC. Certainly, penetration to the viable tissues and beyond represents a loss from the desired deposition site and is counterproductive. Material on top of the skin may be subject to removal by rubbing or contact with water. Ideally, the sunscreens would be bound by the SC, particularly its outer section, so as to immobilize them near the skin surface. With these considerations in mind, we chose the ratio of SC retention to the amount penetrated as an index of skin distribution of sunscreen. The higher this ratio, the better the skin distribution in terms of the function of sunscreen agents. The reason for this phenomenon is not known but it may be rooted in the mutual affinity of the two sunscreens (8). The difference in the ratio between combinations and single sunscreens were greater for benzophenone-3 than OMC. This finding is very important because sunscreens are active within the SC (7) and greater retention by SC increases their efficiency. Therefore, combining different sunscreens in a single preparation not only widens the UV absorption spectrum but may also enhance efficiency.

To conclude, the trends for permeation and skin distribution in micro-Yucatan pig skin agree with reported data for benzophenone-3 and OMC in human skin. Despite the highly lipophilic nature of sunscreens, particularly OMC, SC is the rate limiting skin layer for penetration. Permeation and SC retention were formulation dependent. The ratio of SC content to the amount penetrated, is a useful tool for evaluating sunscreen permeation. The ratios were higher when sunscreens were presented to the skin as a mixture rather than as formulations containing a single sunscreen.

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