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COMMUNICATION

# Effect of the Addition of Oxybenzone or Octyl-Methoxycinnamate on Particle Size of Submicron Emulsions

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**ABSTRACT**

*The formulation of sunscreen products requires understanding of the solubilization of these products in different vehicles to obtain aesthetic preparations and to evaluate long-term stability. For this study, two different ultraviolet (UV) filters were selected: oxybenzone (powder) and octyl-methoxycinnamate (liquid). First, the solubility of these UV filters was tested using a three-component simplex-centroid design strategy. The mixtures were prepared with three oily phases used in this field of cosmetics: liquid paraffin, isopropyl myristate, and coconut oil. A phase diagram method was used to carry out a systematic study of submicron oil-in-water emulsions. Phase diagrams were produced by diluting fixed binary mixtures with water. The surfactant consisted of polyoxyethylene-20-sorbitan monostearate/sorbitan monostearate (50/50, w/w). The oily phase contained equal quantities of each oil studied. From this water/surfactant/oil ternary system, we selected two reference emulsions with receptively 75/5/20 and 68/7/25 proportions. Photon correlation spectroscopy (PCS) was used to investigate the influence of these two UV filters at several concentrations on droplet size and distribution of the oil droplets in the material. All emulsions were stored and checked every month for 6 months.*
***Key Words:*** *Mixture design; PCS; Submicron emulsion; Sunscreen.*

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## INTRODUCTION

Most ultraviolet (UV) filters are insoluble in water, and some are weakly soluble in compatible vehicles used in sunscreens. The formulations most used in this field are water/oil (W/O) or oil/water (O/W) emulsions (1). Emulsions are appreciated since they give uniform and thick sunscreen films. O/W emulsions are very interesting for their appearance on the skin and their greaseless feeling. The low oily phase concentrations used in this field can limit the incorporation of poorly soluble sunscreens. We chose, therefore, to compare two sunscreen agents that are insoluble in water, but with very different oil solubilities, bearing in mind that the addition of UV filters can produce large variation in the stability of the emulsions. To obtain the maximal stability for the reference formulations, we studied submicronic emulsions and the variation in stability generated by the addition of these two filters. By studying the evolution of droplet size, the stability of the emulsion produced can be predicted (2).

## EXPERIMENTAL

### Materials

Liquid paraffin (Primol®, Esso, Paris, France), isopropyl myristate (MIP, Henkel, Düsseldorf, Germany), and coconut oil (Laboratory CPF, Melun, France) were mixed in equal parts. The water used was freshly distilled for formulation of emulsions and sterilized for dilutions (Versol®, Aguettant, Lyon, France). A mixture of two nonionic surfactants was used (50-50, w/w), sorbitan monostearate (Dehymuls SMS®, Henkel) and polyoxyethylene-20-sorbitan (Emulgin SMS20®, Henkel). Two UV filters were studied (Fig. 1). The first was oxybenzone or 2-hydroxy-4-methoxy benzophenone (Eusolex 4360®, Merck, Darmstadt, Germany) presented in the form of crystalline powder with UVB+A sun protection. The second was octyl-methoxycinnamate or 2-ethylhexyl-methoxycinnamate (Parsol MCX®, Givaudan-Roure, Basel, Switzerland), presented in liquid form with UVB protective activity (3).

### Methods

#### Optimization of the Solubilization of Oxybenzone in a Mixture of Oils

The choice of mixture was determined by the dermatological use of the emulsions and by intrinsic advantages of each constituent. Liquid paraffin was used for its neutrality and low cost, MIP because it leaves no sticky or greasy sensation after application, and coconut oil for its vegetable origin and its good compatibility with the skin (4). Octyl-methoxycinnamate is miscible in all proportions with these vehicles, unlike oxybenzone. Using a three-component simplex-centroid design strategy (Scheffé design) (5), we determined the maximum solubility of this UV filter. The simplex-centroid design is a type 1 mixture, and the three factors $X_i$ correspond to the three oily phases. In a $q$-component simplex-centroid design, the number of distinct points is $2^q - 1$. These designs entail testing pure constituents, then three formulations prepared with a 50-50 mixture of each component. A seventh formulation may be prepared with a third part of each component. Three checkpoints used to validate the model are added to these points (numbered 1 to 7). The points corresponding to the different compositions are shown in Fig. 2.

The filter was incorporated into the mixtures with 15 min magnetic stirring, and the preparations were placed in the oven for 2 hr at 60°C ± 2°C. They were then stored for 24 hr at 25°C ± 1°C.

#### Ternary Phase Diagram

A partial phase diagram was produced for the following constituents: a mixture of sorbitan monostearate and polyoxyethylene-20-sorbitan (½, ½ w/w); a mixture of coconut oil, liquid paraffin, MIP (⅓, ⅓, ⅓, w/w/w), and an aqueous phase. The diagram was constructed by suc-

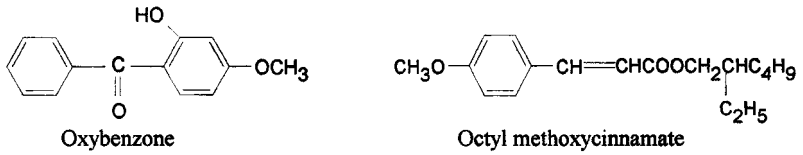


**Figure 1.** Structural diagrams.

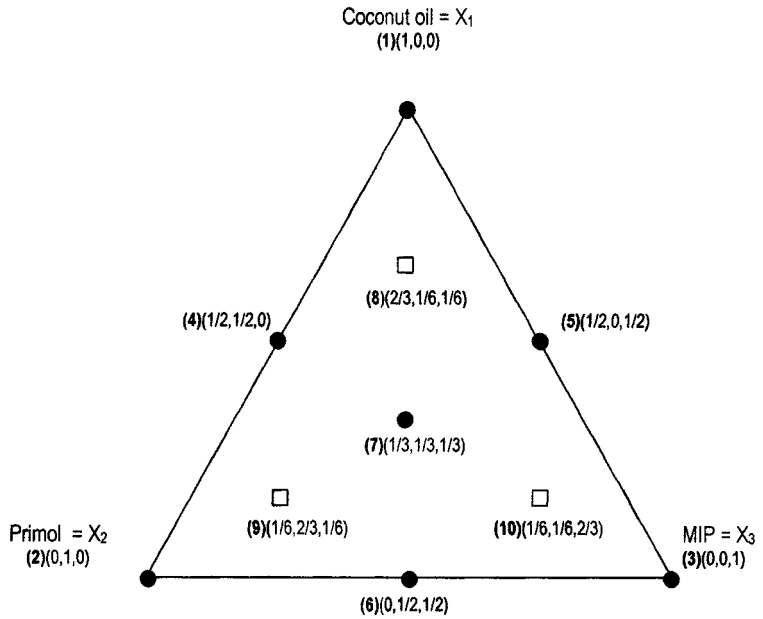


**Figure 2.** Three-component simplex-centroid design. ●, seven design points; and □, three checkpoints.

cessive aqueous dilutions of a binary mixture (surfactants–oily phase). The line represents increasing concentrations of water. Formulation was performed at a temperature of 65°C ± 2°C under agitation with a homogenizer at 400 rpm (Turbotest 33/300, Rayneri, Montreuil, France).

### Formulation of Emulsions

The method of phase inversion was used to prepare selected W/O emulsions. In a preliminary study, the importance of several parameters of oil/water emulsion formulation was evaluated using factorial design (6). Five factors were analyzed: temperature of manufacture, the rate of introduction of one phase into another, the speed of agitation, the mode of cooling, and the operator. The optimum conditions found in this preliminary study produced a rugged formulation method. The conditions were agitation at 400 rpm, temperature 65°C ± 2°C, addition of aqueous phase in 1 min, and cooling to room temperature over 45 min. At first, the droplet size was measured by microscopy. In a second time, only submicron emulsion measurements were made using a SEMATech operating at 632.8 nm with a He-Ne laser as the source of incident light. This instrument was combined with a SEM Real Time Granulometry Correlator (Sematech, Nice, France) using 12 channels, log-log, corresponding to 4096 channels. The emulsions were diluted (10 μl/100 ml) with sterilized water, then transferred to cells immersed in toluene. In each case, analyses were performed in triplicate. The emulsions were diluted because at elevated solute concentrations, the diffusing particles interact with each other, thus modifying the diffusion coefficients (7). All data in the homodyne mode were collected at a scattering angle of 90° at 20°C ± 1°C and analyzed using RTG software to obtain the correlation function, translational diffusion coefficients, and emulsion droplet diameter.

## RESULTS AND DISCUSSION

### Design Evaluation

All the experiments were carried out in random order, and the calculations were performed using Statgraphic software (8). In this three-component simplex-centroid design, 7 design points and 3 checkpoints were generated. The response corresponds to the maximum concentration of filter solubilized. A mathematical model was generated, and we used the model maximizing the value of *R*-square, which is the square of the multiple correlation coefficient. In this case, the special cubic model maximizes *R*-square (0.952). The *R*-square statistic indicates that the model as fitted explains 95.2% of the variability

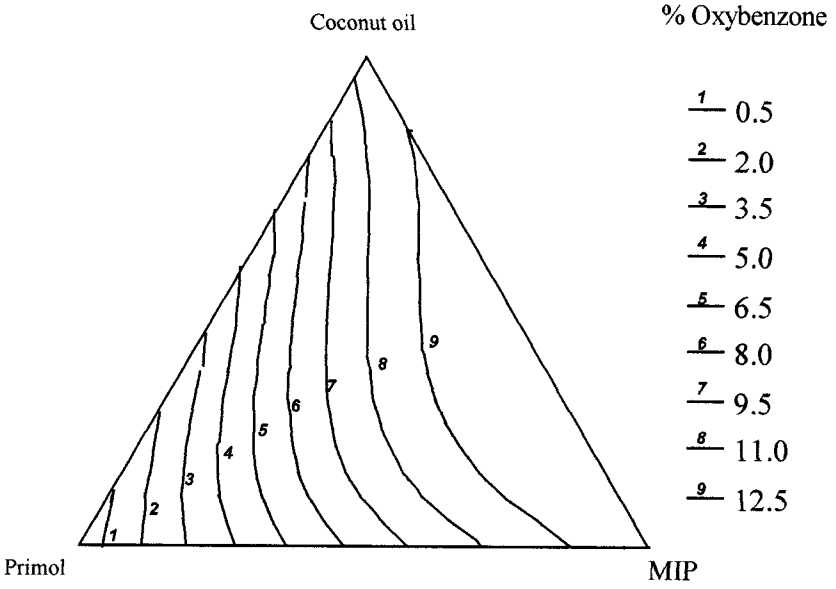


**Figure 3.** Oxybenzone solubilization (%). Contour diagrams obtained from Eq. 1.

in oxybenzone solubility. The equation of this model is as follows:

$$Y = 11.69\,X_1 - 0.23\,X_2 + 13.48\,X_3 - 7.40\,X_1X_2 + 4.35\,X_1X_3 + 7.49\,X_2X_3 + 54.41\,X_1X_2X_3 \quad (1)$$

A response surface is the graph of a system response plotted against the system factor. Therefore, the model is suitable for describing the variables studied. Figure 3 illustrates the contour diagrams obtained from the equation. From this graph, we observe that the mixture of the three oils (⅓⅓⅓) enables 10–11% oxybenzone to be dissolved.

## Determination of Submicron Emulsion Phase Regions

The droplet sizes of all emulsions produced were evaluated in a first step by microscopy select only submicron emulsions. Particle sizing in the submicron range was carried out by photon correlation spectroscopy (PCS), a method of choice in this field. In this study, we obtained the probability of density [$P(D)$] and the mean diameter of the particle population for each sample.

Zones of interest were drawn up from microscope data and PCS data (Fig. 4). A limited zone of submicron emulsions allowed us to select two emulsions. These formulations contained low concentrations of oily phase and surfactants, which corresponds to both a dermatological application and the orientation of the market. Two reference formulations were chosen (emulsion 1 and emulsion 2) and were composed, respectively, of 75/5/20 and 68/7/25 water/surfactants/oils.

## Impact of the Incorporation of Sunscreen Agents into Submicron Emulsions

Preparations of the reference formulations, emulsions 1 and 2, containing from 0.5% to 4% UV filter, were made following the same protocol. Taking account of the proportion of oily phase (20% or 25%), the model predicted a solubility of oxybenzone of 2% in emulsion 1 and 2.5% in emulsion 2. All formulations containing more than these levels showed varying degrees of crystal deposition. It should be noted that emulsification does not increase the solubility compared to the model realized previously. Only emulsions free of crystal deposits were studied. Each emulsion was analyzed in triplicate at day 7. All data were treated by a nonlinear regression with the Gauss-Newton method (9).

The mean droplet diameter, dispersion, and indication of polydispersity are presented for each emulsion in Tables 1 and 2. According to international standards, the two parameters describing particle size distribution (i.e.,

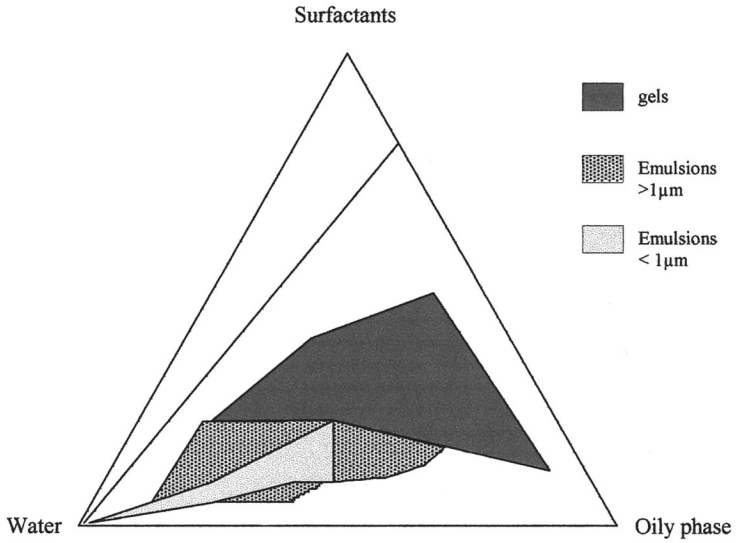


**Figure 4.** Zones of interest analyzed with microscope data and PCS data.

the average PCS mean diameter and the polydispersity index) constitute the so-called cumulant method. The polydispersity index (PI) was calculated according to the International Organization for Standardization (ISO) 13321. PI is a dimensionless measure of the broadness of size distribution. Measurement of the definite diameter latex (497 nm) following the same protocol gave us a diameter of 497.7 nm (with a dispersion of 186.1 nm and PI of 0.10).

Theoretical curves were calculated for all emulsions (nonlinear regression). Experimental and theoretical data for the two reference emulsions are showed in Fig. 5. These submicron emulsions are characterized as follows: Emulsion 2 (droplet diameter 271.5 nm) was finer than emulsion 1 (droplet diameter 321.8 nm). The dispersion decreased in a similar manner: 158.8 nm for emulsion 1 and 115 nm for emulsion 2.

## Influence of the Variation in Oxybenzone Concentration

In both studies, the relationship between variables $X$ and $Y$ ($X$ = concentration of added oxybenzone, and

***Table 1***

*Characteristics of Emulsions 1*

| Emulsions 1 | Mean Diameter of Droplets (nm) | Dispersion (nm) | PI |
|---|---|---|---|
| **Emulsion 1 (reference)** | **321.8** | **158.8** | **0.15** |
| 0.5% Oxybenzone | 312.4 | 165.4 | 0.17 |
| 1% Oxybenzone | 315.5 | 195.0 | 0.21 |
| 1.5% Oxybenzone | 282.7 | 144.0 | 0.16 |
| 2% Oxybenzone | 278.2 | 137.2 | 0.15 |
| 0.5% O. methoxycinnamate | 341.0 | 184.1 | 0.17 |
| 1% O. methoxycinnamate | 309.8 | 164.0 | 0.17 |
| 2% O. methoxycinnamate | 327.4 | 191.0 | 0.19 |
| 2.5% O. methoxycinnamate | 330.8 | 212.4 | 0.22 |
| 3% O. methoxycinnamate | 355.1 | 236.8 | 0.23 |
| 3.5% O. methoxycinnamate | 335.8 | 207.6 | 0.21 |
| 4% O. methoxycinnamate | 364.3 | 272.0 | 0.27 |

***Table 2***

*Characteristics of Emulsions 2*

| Emulsions 2 | Mean Diameter of Droplets (nm) | Dispersion (nm) | PI |
|---|---|---|---|
| **Emulsions 2 (reference)** | **271.5** | **115.4** | **0.12** |
| 0.5% Oxybenzone | 279.9 | 142.5 | 0.16 |
| 1% Oxybenzone | 256.2 | 120.5 | 0.14 |
| 1.5% Oxybenzone | 250.4 | 115.4 | 0.14 |
| 2% Oxybenzone | 242.1 | 116.0 | 0.15 |
| 2.5% Oxybenzone | 249.1 | 126.8 | 0.16 |
| 0.5% O. methoxycinnamate | 260.6 | 122.5 | 0.14 |
| 1% O. methoxycinnamate | 247.5 | 103.0 | 0.12 |
| 1.5% O. methoxycinnamate | 239.6 | 122.0 | 0.17 |
| 2% O. methoxycinnamate | 273.5 | 109.2 | 0.11 |
| 2.5% O. methoxycinnamate | 268.2 | 126.1 | 0.14 |
| 3% O. methoxycinnamate | 286.3 | 134.7 | 0.14 |
| 3.5% O. methoxycinnamate | 283.0 | 138.5 | 0.15 |
| 4% O. methoxycinnamate | 271.0 | 117.5 | 0.13 |

$Y$ = mean droplet diameter) is a simple linear regression (Fig. 6).

For emulsion 1, the equation of the fitted model is

$$Y = -23.36X + 325.52 \quad (2)$$

The regression coefficient (slope) differs significantly from zero (two-tailed test, $p = .027$).

For emulsion 2, the model is defined by the equation

$$Y = -13.19X + 274.72 \quad (3)$$

and the slope differs significantly from zero (two-tailed test, $p = .031$).

Both slopes were therefore significantly different from zero, and both were negative. The relationship between $Y$ and $X$ decreases, which demonstrates that the oxybenzone has a statistically significant tendency to decrease the diameter of droplets in the two types of emulsions. This evolution is interesting since it reveals the best stability of the emulsion. We can observe that for emulsion 1 the slope is greater than for emulsion 2. A notable variation of the dispersion or the polydispersity index does not follow a reduction in droplet size. These formulations will not allow very high concentrations of oxybenzone since increasing in concentration of

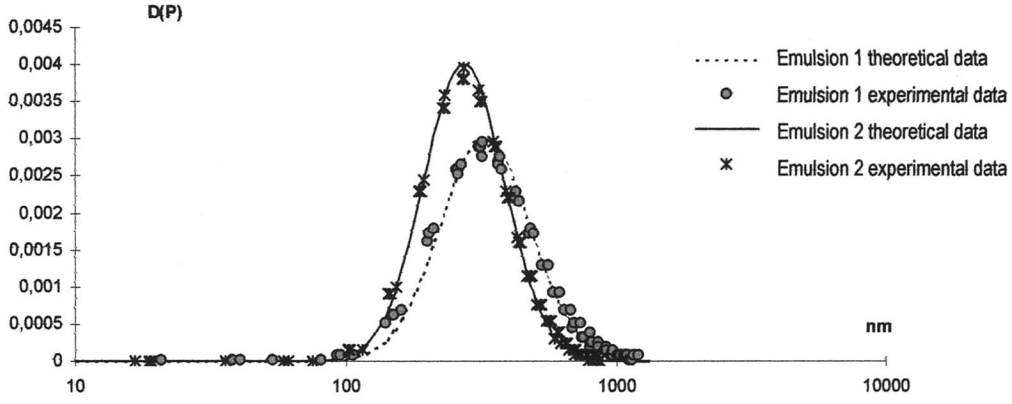


**Figure 5.** Experimental and theoretical data of the two emulsions (without oxybenzone).

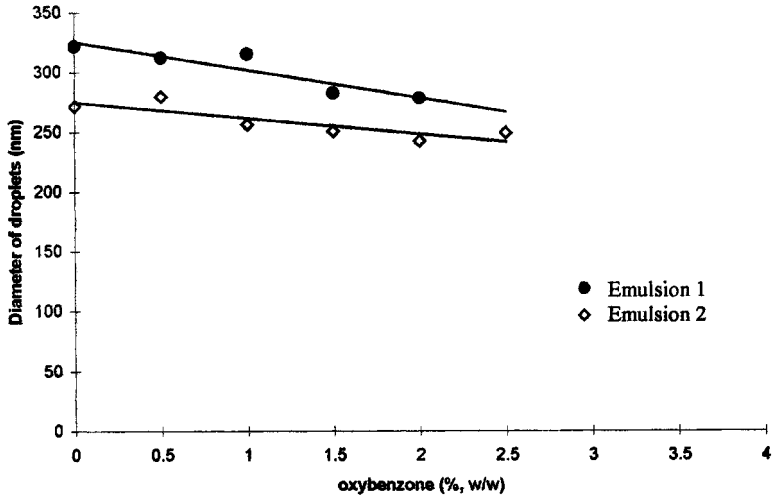


**Figure 6.** Influence of the variation of oxybenzone concentration on droplet size.

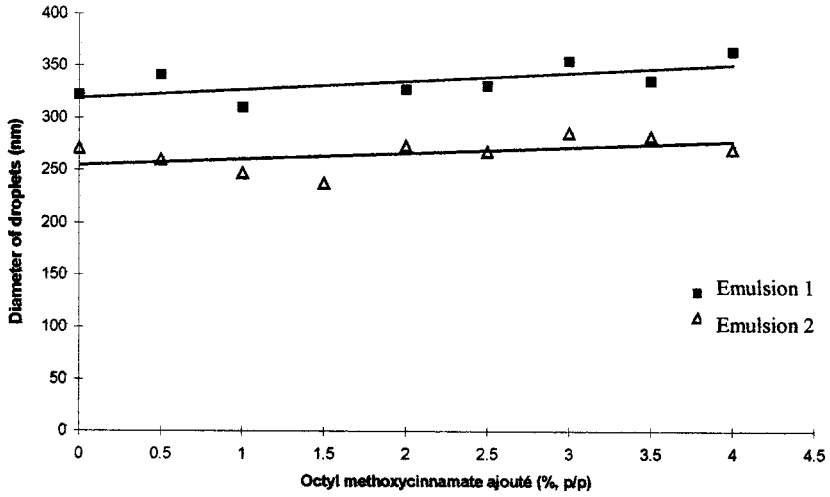


**Figure 7.** Influence of the variation of octyl-methoxycinnamate concentration on droplet size.

this filter led very quickly and invariably to its recrystallization.

### Influence of the Variation in Octyl-Methoxycinnamate Concentration

For both types of emulsion, the addition of octyl-methoxycinnamate did not significantly modify the mean droplet diameters in these formulations (Fig. 7) (two-tailed test, slopes not significantly different from zero). On the other hand, dispersion was increased in type 1 emulsions, as was the indication of polydispersity, which could lead in the long term to a decrease in stability; the different products do not show signs of macroscopic instability.

## REFERENCES

1. K. Klein, Formulation sunscreens, in *Sunscreens Development, Evaluation and Regulatory Aspects* (N. L. Lowe and

N. A. Shaath, Eds.), Marcel Dekker, New York, 1996, pp. 235–266.
2. G. Mestres, F. Nieloud, R. Fortuné, J. M. Devoisselle, R. Marti, and G. Mestres, Drug Dev. Ind. Pharm., 22(12), 1193–1199 (1996).
3. K. Klein, Cosmet. Toil., 107, 45–64 (1992).
4. G. H. Dahms, Cosmet. Toil., 109, 45–52 (1994).
5. J. A. Cornell, *Experiments with Mixtures*, John Wiley and Sons, New York, 1990.
6. F. Nielloud, G. Marti-Mestres, J. P. Laget, C. Fernandez, and H. Maillols, Drug Dev. Ind. Pharm., 22, 159–166 (1996).
7. G. D. J. Phillies, Quasielastic light scattering, Anal. Chem., 62(20), 1049A–1057A (1990).
8. Manugistics, *Statgraphic plus*, Author, MD, 1995.
9. A. Antoniadis, J. Berruyer, and R. Carmona, *Régression non linéaire et applications*, Economica, Paris, 1992.