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Stability of ascorbyl palmitate in topical microemulsions

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Abstract

Ascorbyl palmitate and sodium ascorbyl phosphate are derivatives of ascorbic acid, which differ in stability and hydro-lipophilic properties. They are widely used in cosmetic and pharmaceutical preparations. In the present work the stability of both derivatives was studied in microemulsions for topical use as carrier systems. The microemulsions were of both o/w and w/o types and composed of the same ingredients. The stability of the less stable derivative ascorbyl palmitate was tested under different conditions to evaluate the influence of initial concentration, location in microemulsion, dissolved oxygen and storage conditions. High concentrations of ascorbyl palmitate reduced the extent of its degradation. The location of ascorbyl palmitate in the microemulsion and oxygen dissolved in the system together significantly influence the stability of the compound. Light accelerated the degradation of ascorbyl palmitate. In contrast, sodium ascorbyl phosphate was stable in both types of microemulsions. Sodium ascorbyl phosphate is shown to be convenient as an active ingredient in topical preparations. In the case of ascorbyl palmitate, long-term stability in selected microemulsions was not adequate. To formulate an optimal carrier system for this ingredient other factors influencing the stability have to be considered.

Keywords: Ascorbyl palmitate; Sodium ascorbyl phosphate; Stability; Microemulsions; Topical

1. Introduction

Vitamin C (L-ascorbic acid) has been used in cosmetic and dermatological products since it has many favourable effects on the skin (Silva and Maia Campos, 2000). As a reducing agent, vitamin C can scavenge and destroy aggressive oxidizing agents and radicals. Because of its capability to suppress pigmentation of the skin and decomposition of melanin it can be used to whiten the skin. Vitamin C also improves the elasticity of the skin by promoting the formation of collagen (Darr et al., 1992; Djerassi, 1997; Fox, 1997).

The use of ascorbic acid in cosmetic and pharmaceutical products is however limited due to its low stability. Under aerobic conditions it is reversibly oxidized to L-dehydro ascorbic acid, which can be irreversibly degraded to oxalic acid (Kleszczewska, 2000). To solve this problem of stability, derivatives of vitamin C have been synthesized having an action similar to ascorbic acid but with improved chemical stability. Two derivatives are widely used in cosmetic products:

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lipophilic ascorbyl palmitate and hydrophilic ascorbyl phosphate salts. These differ in their ability to permeate the skin, as a result of their different hydro-lipophilic properties. Because of its lipophilic character ascorbyl palmitate penetrates more easily, while ascorbyl phosphate salts, being prodrugs, must be converted by an enzymatic hydrolytic process before penetrating in the skin. These two derivatives also differ in stability (Austria et al., 1997; Silva and Maia Campos, 2000).

According to literature data, magnesium ascorbyl phosphate is more stable than ascorbyl palmitate in solutions and topical formulations. The stability of ascorbyl palmitate also depends on the structural properties of the formulations (Austria et al., 1997). We have therefore investigated the influence of different parameters on the stability of ascorbyl palmitate, and tested the stability of the hydrophilic derivative sodium ascorbyl phosphate in the same formulations.

We have chosen microemulsions as carrier systems because of their thermodynamic stability and simple technology of preparation. These systems have also high solubilizing power, so that large amounts of poorly soluble compounds can be included (Eccleston, 1994; Neubert et al., 1998; Terjarla, 1999). After application onto the skin, components of the microemulsions interact with the intercellular lipids of the skin. The intercellular space is changed, so drug transport is facilitated (Delgrado-Charo et al., 1997; Schmalfuss et al., 1997).

Both derivatives were included in o/w as well as in w/o microemulsions. Lipophilic ascorbyl palmitate was incorporated in the internal phase of o/w and in the external phase of w/o microemulsions. Hydrophilic sodium ascorbyl phosphate was deposited in the corresponding aqueous phases.

The aim of this work was to investigate the stability of the two ascorbic acid derivatives in each phase of two microemulsion types. Secondly, the influence of other parameters, including light, initial concentration and degassing of samples, on the degradation of the less stable ascorbyl palmitate was determined.

2. Materials and methods

2.1. Materials

Ascorbyl palmitate was provided by Hoffmann La Roche (Switzerland) and sodium ascorbyl phosphate by BASF (Germany). Their chemical structures are shown in Fig. 1. The microemulsions consisted of the caprylic/capric triglyceride, Mygliol 812 (Hüls, Germany), as oil phase; the PEG-8 caprylic/capric glycerides, Labrasol (Gattefosse, France), as surfactant; the polyglyceryl-6 dioleate, Plurol oleique (Gattefosse, France), as cosurfactant and water as hydrophilic phase. The water was prepared by distillation of reverse osmosis water.

2.2. Preparation of microemulsions

Active ingredients were incorporated into microemulsions at concentrations of 0.25–2.00 w/w% concentrations. The active compound was dissolved in the component with the highest solubility, then the other three components were added. Ascorbyl palmitate is most soluble in Labrasol and sodium ascorbyl phosphate in

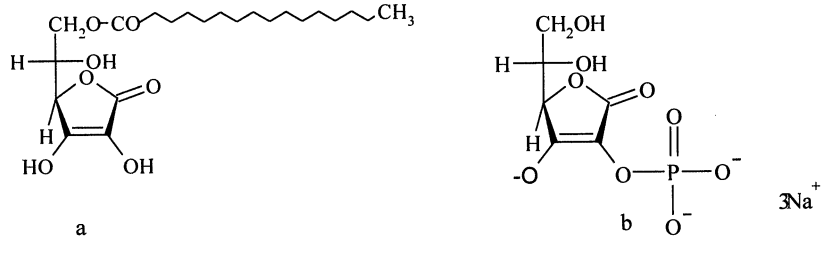

Fig. 1. Chemical structures of ascorbyl palmitate (a) and sodium ascorbyl phosphate (b).

Table 1
The composition of w/o and o/w microemulsions (w/w percent)

Component	w/o	o/w
Caprylic/capric triglyceride	24.75%	7.43%
PEG-8 caprylic/capric glycerides	47.53%	38.02%
Polyglyceryl-6 dioleate	11.88%	9.50%
Purified water	15.84%	45.05%

purified water (Špiclin and Gašperlin, 1999). Microemulsions were formed spontaneously after gentle hand mixing. The quantitative compositions of both types of microemulsion are shown in Table 1.

2.3. Stability studies

All samples were stored in well-closed 25 ml glass flasks. During storage samples were kept at room temperature (22 ± 1 °C) in the dark, except for those used for studying the influence of light. The amount of nondegraded active ingredient in samples was determined quantitatively at the beginning of storage and subsequently on the 1st, 2nd, 3rd, 7th, 14th and 28th day.

2.4. Apparatus

The HPLC apparatus consisted of Knauer HPLC pump 64, a sample injector Rheodyne 7125 with a 20 μl sample loop and a Knauer variable wavelength detector.

2.5. Chromatographic conditions

1. For ascorbyl palmitate the stationary phase was a 120×4 mm ID column packed with 5 μm Eurospher C 18, the mobile phase methanol-acetonitrile-0.02 M phosphate buffer pH 2.5 (75:10:15). The flow rate was 1.5 ml min^{-1} and UV detection at 254 nm.
2. For sodium ascorbyl phosphate the stationary phase was a 250×4 mm ID column packed with 100 μm Nucleosil NH_2, the mobile phase acetonitrile-0.3 M phosphate buffer pH 4 (40:60). The flow rate was 0.8 ml min^{-1} and UV detection at 258 nm.

All analyses were performed at ambient temperature.

2.6. Sample preparation

For ascorbyl palmitate 100 μl of microemulsion were diluted 1:100 (v/v) with methanol; for sodium ascorbyl phosphate 100 μl of microemulsion were diluted 1:100 (v/v) with tetrahydrofuran-0.3 M phosphate buffer pH 4 and then further diluted with 0.3 M phosphate buffer pH 4 to a final dilution 1:1000 (v/v).

3. Results and discussion

3.1. Chromatographic analysis of ascorbyl palmitate and sodium ascorbyl phosphate in microemulsions

Several chromatographic analytical methods for quantifying the amount of ascorbyl palmitate and ascorbyl phosphate salts are described in the literature. Ascorbyl palmitate has been determined using amino (Austria et al., 1997; Cahuk and Krbavcic, 2000) and cyano-propyl columns (Sottofattori et al., 1998). However, none of them was optimal for determining ascorbyl palmitate in selected microemulsions. We used therefore different chromatographic conditions as described in Section 2.5, which proved to be suitable for systems under study. Sodium ascorbyl phosphate was determined as described previously (Austria et al., 1997). Fig. 2 shows the chromatographic patterns for both compounds under the cited chromatographic conditions. Calibration curves were linear in the interval tested using five points with three replicates. The correlation coefficients of the corresponding regression lines were greater than 0.999 for both compounds.

3.2. Stability of ascorbyl palmitate in microemulsions

The instability of ascorbyl palmitate is a result of its oxidative degradation. Generally, the kinet-

ics of oxidative reactions are second order, but can usually be simplified to pseudo first order if oxygen is in excess. The reactions are catalyzed by metal ions and/or by light. They also occur in larger extent in more dilute systems, indicating that the initial concentration of the active ingredient is an important factor concerning the extent of its degradation (Carstensen, 2000a,b). The influence of the initial concentration of ascorbyl palmitate on its stability for two selected systems was therefore studied at the beginning of our work. It is known that the concentration range of ascorbyl palmitate is on general from 0.05 to 0.1%, when used as an antioxidant to stabilize formulation; if used as an active ingredient the concentrations are higher, usually 1–2%. In our study, ascorbyl palmitate was incorporated in both types of microemulsion in concentrations 0.25, 0.50, 0.75, 1.00, 1.50 and 2.00%. Fractions of nondegraded ascorbyl palmitate determined at different time intervals of storage in the dark are listed in Table 2 and plotted in Fig. 3. As seen from Fig. 3 the degradation of ascorbyl palmitate was large in both types of microemulsion. After 28 days less than 40% of active ingredient remained in all samples. It was further confirmed that the initial concentration significantly influences the degradation of the compound, higher concentrations of ascorbyl palmitate as a rule reducing the extent of its degradation.

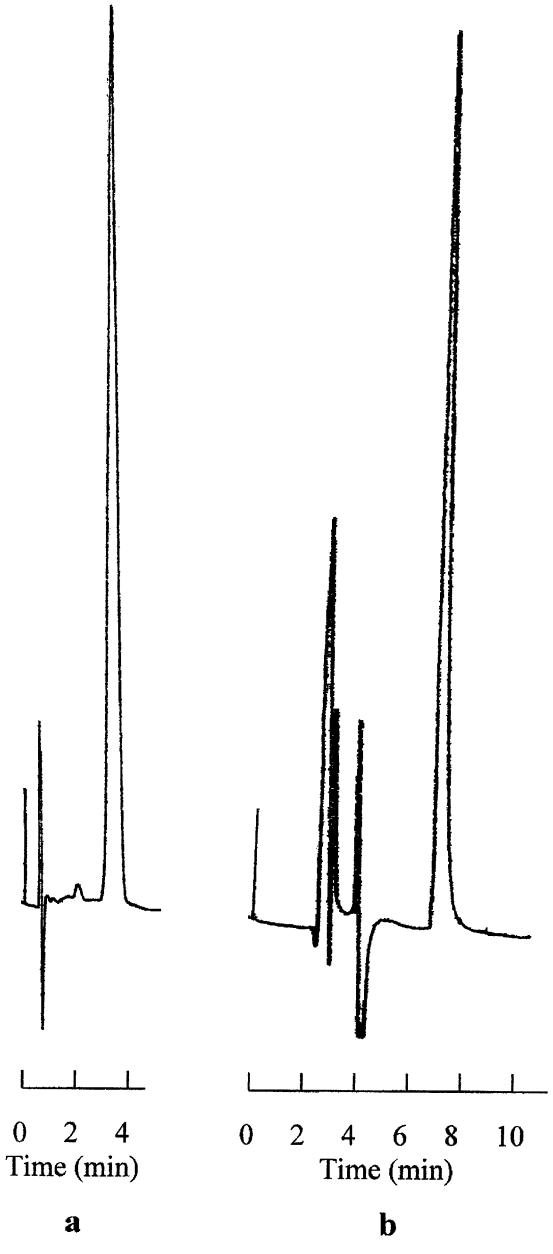

Fig. 2. HPLC chromatogram of microemulsion with ascorbyl palmitate (a) and sodium ascorbyl phosphate (b) at conditions described in Section 2.

Degradation profiles of ascorbyl palmitate were evaluated by fitting experimental data to different order kinetics. The data were transformed for linear regression analysis for zero, first and simple second order reactions. The calculated Pearson values are listed in Table 3, bold print indicating best fits. At high ascorbyl palmitate concentrations we found that the degradation was a second order reaction described by the general rate equation: $-\mathrm{d}[A]/\mathrm{d}t = k_2[A][\mathrm{O}_2]$ assuming equal initial concentrations of active compound and the dissolved oxygen. At these initial concentrations there was evidently no excess of oxygen over ascorbyl palmitate. On the other hand, at low concentrations of active ingredient, oxygen was abundant compared to ascorbyl palmitate, reducing the order of these reactions to pseudo-first order, described by $-\mathrm{d}[A]/\mathrm{d}t = k_1'[A]$. As can be seen from Table 3 the alternation from second to pseudo-first order occurs at concentration 0.50% in w/o type and at concentration 1.00% in o/w type of microemulsions. Considering pseudo-first

Table 2
Percentages of nondegraded ascorbyl palmitate ($n = 3$) in w/o and o/w microemulsions at different initial concentrations in the dark

	Day						
Sample[a]	0	1	2	3	7	14	28
w/o-2.00%	100	92.05 ± 2.85	84.70 ± 3.32	72.94 ± 3.01	69.32 ± 3.35	56.26 ± 1.36	36.25 ± 1.71
w/o-1.50%	100	93.53 ± 1.97	82.96 ± 2.14	70.98 ± 1.78	64.94 ± 3.03	47.50 ± 2.08	29.23 ± 0.81
w/o-1.00%	100	78.35 ± 2.55	68.54 ± 1.44	62.07 ± 1.84	47.25 ± 1.95	31.95 ± 1.70	19.02 ± 0.50
w/o-0.75%	100	82.46 ± 2.82	73.02 ± 1.75	63.86 ± 1.10	45.47 ± 2.03	27.89 ± 1.35	13.89 ± 0.90
w/o-0.50%	100	78.98 ± 5.91	72.22 ± 5.61	64.81 ± 7.96	40.19 ± 6.26	20.71 ± 5.04	6.25 ± 1.11
w/o-0.25%	100	75.10 ± 1.41	56.63 ± 3.56	50.41 ± 3.69	23.09 ± 2.16	5.41 ± 0.10	0.00
o/w-2.00%	100	92.13 ± 7.85	87.71 ± 9.47	75.01 ± 10.62	51.03 ± 5.78	36.74 ± 1.39	28.46 ± 1.26
o/w-1.50%	100	87.45 ± 6.79	74.35 ± 11.10	30.03 ± 10.30	35.19 ± 7.45	21.77 ± 2.90	16.10 ± 1.54
o/w-1.00%	100	101.11 ± 2.16	92.81 ± 4.04	85.52 ± 2.67	55.87 ± 1.97	41.49 ± 2.81	12.83 ± 1.03
o/w-0.75%	100	90.05 ± 7.49	76.57 ± 10.20	64.83 ± 13.42	30.32 ± 11.89	13.46 ± 7.05	3.94 ± 0.97
o/w-0.50%	100	87.41 ± 5.00	67.51 ± 15.14	53.49 ± 16.15	20.20 ± 10.96	4.06 ± 2.59	–[b]
o/w-0.25%	100	77.00 ± 8.07	55.29 ± 13.91	30.83 ± 8.84	7.61 ± 5.81	0.00	0.00

[a] Percentage in the name of sample means w/w% of ascorbyl palmitate in microemulsion.
[b] Measurement was not carried out.

order in the case of oxygen being in excess over ascorbyl palmitate we can conclude that in o/w microemulsions oxygen is in excess at higher initial concentrations of ascorbyl palmitate than in w/o microemulsions, which indicates the different abilities of the two microemulsions to dissolve oxygen.

These observations raise the question as to whether the location of active ingredient in a microemulsion could influence its stability toward oxidation. When we compared the rates of degradation of ascorbyl palmitate at the same initial concentration in both types of microemulsions, it was evident that the type of microemulsion significantly influences the stability (Fig. 4). Significant differences were proved using Student's t-test at α 0.05. As shown in Fig. 4 we found that ascorbyl palmitate was more stable in w/o microemulsions. The differences became significant after 1 week for most initial concentrations except for 0.25% and 1.00% (Table 2). At the lowest initial concentration examined, 0.25%, differences became significant earlier, consistent with the fact that oxidative reactions occur to a larger extent in more dilute systems. Despite the fact that the difference in the case of 1.00% was found significant later, probably because of experimental deviations, the degradation pattern of all initial concentrations became uniform after a large extent of degradation.

The higher stability of ascorbyl palmitate in w/o microemulsions can be explained as a consequence of different partition patterns of ascorbyl palmitate in w/o and o/w microemulsions. Due to their chemical structure the molecules of ascorbyl palmitate are orientated at the w/o interface with the palmitic residue in the lipophilic phase and the cyclic ring in the aqueous phase. Only the cyclic ring is sensitive to oxidation. In w/o microemulsions this part of the molecule is located in the internal aqueous phase, while in o/w microemulsions it is in the external aqueous phase. Although oxygen is more soluble in the external oil phase of w/o microemulsions than in the external aqueous phase of o/w microemulsions, the degradation of ascorbyl palmitate is higher in the latter, because in w/o microemulsions the w/o interface act as a barrier for the diffusion of oxygen to the internal aqueous phase (Gallarate et al., 1999). In w/o microemulsions the cyclic ring is oxidized by the limited amount of oxygen dissolved in the internal aqueous phase before the preparation of microemulsions. The w/o interface prevents further diffusion of oxygen from the external to the internal phase of w/o microemulsions. On the contrary, in o/w microemulsions the dissolution of oxygen

from the outside compensates for the oxygen consumed in the degradation reactions. That is why, in the case of o/w microemulsions, the oxygen is in excess at higher concentrations of ascorbyl palmitate than in w/o microemulsions.

To eliminate the influence of oxygen, the stability of ascorbyl palmitate was determined in microemulsions in which oxygen was removed by argon flooding. Argon was chosen because it is inert and heavier than air. Results are listed in Table 4 and the fraction of nondegraded ascorbyl palmitate plotted as a function of time in microemulsions with and without degassing at 2.00% initial concentration in Fig. 5. Based on statistical analysis several conclusions can be drawn. Both systems, when flooded with argon, were more stable than in the absence of degassing. However, the effect on stability is more prominent in the case of o/w microemulsions. Differences became significant after the third day confirmed by t-test at α 0.05. On the contrary, the stability of the compound was not significantly influenced by argon flooding in w/o microemulsions. This is in

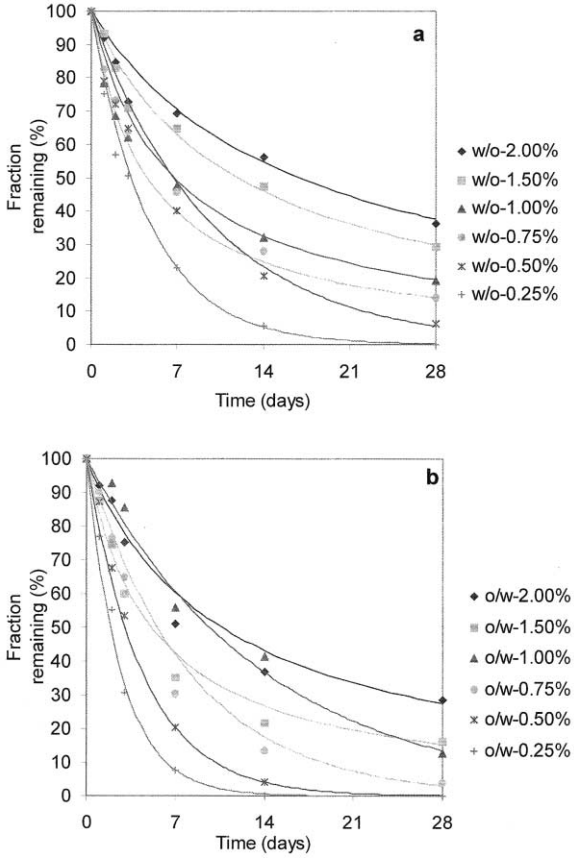

Fig. 3. Degradation of ascorbyl palmitate at different initial concentrations in w/o (a) and o/w (b) microemulsions in the dark. The experimental data are fitted second order rate equation for w/o-2.00%, w/o-1.50%, w/o-1.00%, w/o-0.75%, o/w-2.00%, o/w-1.50% and first order rate equation for w/o-0.50%, w/o-0.25%, o/w-1.00%, o/w-0.75%, o/w-0.50%, o/w-0.25%.

Table 3
Pearson coefficients for the case of zero, first and second order reactions at different initial concentrations

Sample	Zero order[a]	First order[b]	Second order[c]
w/o-2.00%	−0.9442	−0.9809	**0.9916**
w/o-1.50%	−0.9384	−0.9838	**0.9959**
w/o-1.00%	−0.8852	−0.9708	**0.9992**
w/o-0.75%	−0.9041	−0.9844	**0.9959**
w/o-0.50%	−0.9084	**−0.9965**	0.9681
w/o-0.25%	−0.8345	**−0.9987**	0.9531
o/w-2.00%	−0.8931	−0.9432	**0.9796**
o/w-1.50%	−0.8471	−0.9297	**0.9816**
o/w-1.00%	−0.9602	**−0.9956**	0.9602
o/w-0.75%	−0.8782	**−0.9889**	0.9711
o/w-0.50%	−0.9310	**−0.9996**	0.9469
o/w-0.25%	−0.7437	**−0.9966**	0.9627

[a] Represents the extent of a linear relationship between A_t and t;
[b] Represents the extent of a linear relationship between $\ln A_t$ and t;
[c] Represents the extent of a linear relationship between $1/A_t$ and t; where A_t is a fraction of nondegraded ascorbyl palmitate.

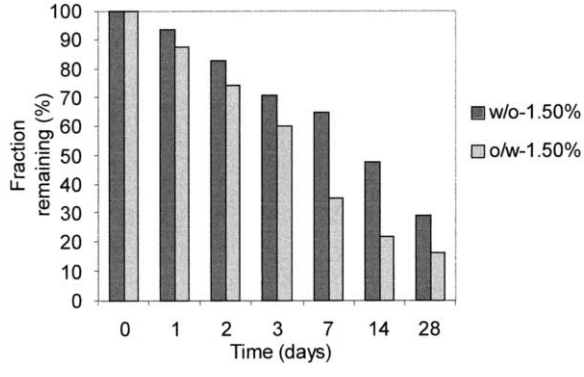

Fig. 4. Degradation of ascorbyl palmitate at initial concentration 1.50% in w/o and o/w microemulsion.

Table 4
Percentages of nondegraded ascorbyl palmitate ($n = 3$) in degassed w/o and o/w microemulsions

	Day						
Sample[a]	0	1	2	3	7	14	28
w/o-degas	100	88.51 ± 3.02	89.36 ± 4.18	83.17 ± 5.23	75.18 ± 5.55	60.58 ± 16.18	39.89 ± 8.16
o/w-degas	100	99.34 ± 3.70	101.48 ± 3.49	90.63 ± 1.27	91.63 ± 0.39	79.39 ± 11.99	53.23 ± 10.08

[a] Percentage in the name of sample means w/w% of ascorbyl palmitate in microemulsion.

accordance with our previous assumption that the instability of ascorbyl palmitate is highly dependent on the oxygen dissolved in the aqueous phase. It is more difficult to degas the internal aqueous phase of w/o microemulsions than that of o/w microemulsions, because of the w/o interface. The significantly greater effect on stability of ascorbyl palmitate in degassed o/w compared to degassed w/o microemulsion is consistent with this finding. There is also a second effect, which could contribute to these results. One possible explanation as to what happened in the system is seen from an analysis of its composition. Because ascorbyl palmitate is soluble only in the oil phase and in the surfactants (Špiclin and Gašperlin, 1999), we can calculate an approximate available volume for the partition of ascorbyl palmitate from the quantitative composition of microemulsions (Table 1). The compound can take approximately up to 85% volume of w/o and 55% volume of o/w microemulsion, assuming that all components have similar densities. This shows that at the same initial concentration of ascorbyl palmitate in w/o and o/w microemulsions the compound is more concentrated in the latter. Higher local concentrations may increase its stability toward oxidation. However this assumption has to be confirmed by more detailed study of the microemulsion structure.

It is well known that the light is also an important factor that induces many oxidative reactions, mainly through formation of free radicals followed by chain reactions. The influence of light was therefore an important part of stability evaluation of the ascorbyl palmitate in microemulsions. The experiment was performed in w/o microemulsions because they have a higher content of oil phase, which is the more sensitive to light. Again the experiment was carried out at different initial concentrations: 1.00%, 0.75%, 0.50% and 0.25%. Samples were stored in well-closed, transparent glass flasks and exposed to daylight. Samples exposed to daylight were less stable than those stored in the dark (Tables 2 and 5). At initial concentrations lower than 1.00%, differences were already significant ($\alpha = 0.05$) by the first day of storage. At 1.00% initial concentration the differences took longer to become significant. The rates of reaction in 1.00% microemulsions stored in the dark and in the daylight were plotted according to second order equations. The rate of degradation in the light was faster (Fig. 6), with slopes for samples stored in the dark and in the daylight of 0.015 and 0.02 $days^{-1}$ respectively.

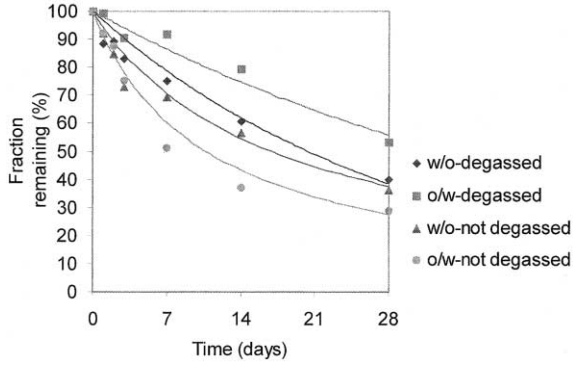

Fig. 5. The influence of degassing on the stability of ascorbyl palmitate at an initial concentration of 2.00% for w/o and o/w microemulsions.

Table 5
Percentages of nondegraded ascorbyl palmitate ($n = 3$) in w/o microemulsions exposed to daylight at different initial concentrations.

	Day						
Sample[a]	0	1	2	3	7	14	28
w/o-1.00%	100	80.82 ± 15.08	72.21 ± 10.35	63.50 ± 10.14	45.58 ± 6.50	30.89 ± 3.88	14.58 ± 1.93
w/o-0.75%	100	67.58 ± 5.09	58.77 ± 5.17	49.52 ± 0.80	28.91 ± 8.15	15.19 ± 7.49	4.16 ± 3.62
w/o-0.50%	100	55.01 ± 7.02	49.15 ± 3.15	39.74 ± 4.21	21.58 ± 3.72	9.34 ± 2.26	–[b]
w/o-0.25%	100	48.27 ± 7.82	35.72 ± 3.05	24.14 ± 0.29	8.45 ± 0.76	0.00	0.00

[a] Percentage in the name of sample means w/w% of ascorbyl palmitate in microemulsion.
[b] Measurement was not carried out.

3.3. Stability of sodium ascorbyl phosphate in microemulsions

According to the literature and to the producer specification ascorbyl phosphate salts are among the most stable ascorbic acid derivatives. The stability is a result of its chemical structure. Introduction of the phosphate group in the second position of the cyclic ring protects the enediol system of the molecule from oxidation, so that ascorbyl phosphate salts are not antioxidant agents (Austria et al., 1997). To achieve this function the compound has to be converted to free vitamin C by enzymes present in the skin. Because of this sodium ascorbyl phosphate cannot act as an antioxidant to stabilize formulations. We tested its stability in the dark in both microemulsions at an initial concentration 1.00%, the fractions of nondegraded sodium ascorbyl phosphate being determined by HPLC. As expected, sodium ascorbyl phosphate was stable in both types of microemulsion with no significant difference between the two. Compared to ascorbyl palmitate, sodium ascorbyl phosphate was significantly more stable. After 2 months, more than 95% of nondegraded compound remained in both microemulsions. These results support the use of sodium ascorbyl phosphate as an active ingredient in cosmetic and pharmaceutical preparations.

4. Conclusions

The stability of ascorbyl palmitate and sodium ascorbyl phosphate has been determined in microemulsions of different type. As expected, the hydrophilic sodium ascorbyl phosphate is more stable than the lipophilic ascorbyl palmitate. The stability of ascorbyl palmitate is highly dependent on its initial concentration, its location in the microemulsion, the amount of oxygen dissolved in the system and the storage conditions. The compound is most stable at the highest initial concentration used—2.00%. If oxygen is not removed from carrier system, the compound is more stable in w/o microemulsions; on the contrary if microemulsions are degassed, the compound is more stable in the o/w type. Light accelerates the oxidative degradation of ascorbyl palmitate.

Although ascorbyl palmitate is more convenient for topical application than sodium ascorbyl phosphate, because of its lipophilic character, which contributes to its penetration in the skin, its

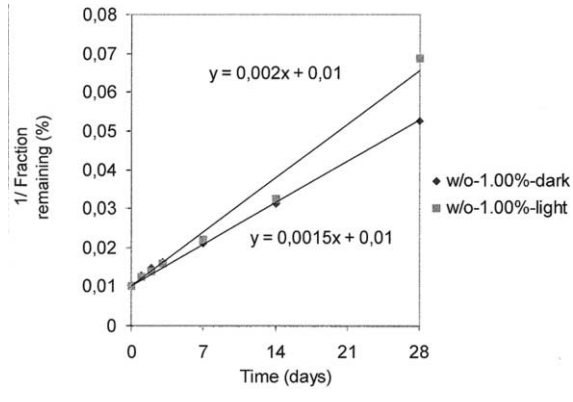

Fig. 6. Second order rate plot for the degradation of ascorbyl palmitate with time for 1.00% w/o microemulsion stored in the dark and in daylight.

long-term stability in formulations is not adequate. Possible approaches to increase its stability are proper selection of type of microemulsion, and appropriate choice of initial concentration and storage conditions. Other factors also have to be considered in formulating an optimal microemulsion as carrier for ascorbyl palmitate for topical use, for example the selection of non-oxidizable components of the carrier system. Nevertheless ascorbyl palmitate is still convenient as an antioxidant to stabilize formulation.

On the contrary sodium ascorbyl phosphate can be used as an active ingredient in cosmetic and pharmaceutical preparations on the basis of its stability. Because it is hydrophilic the selection of proper carrier system is important to achieve maximal penetration in the skin.

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