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Sodium ascorbyl phosphate in topical microemulsions

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Abstract

Sodium ascorbyl phosphate is a hydrophilic derivative of ascorbic acid, which has improved stability arising from its chemical structure. It is used in cosmetic and pharmaceutical preparations since it has many favorable effects in the skin, the most important being antioxidant action. In order to achieve this, it has to be converted into free ascorbic acid by enzymatic degradation in the skin. In the present work, o/w and w/o microemulsions composed of the same ingredients, were selected as carrier systems for topical delivery of sodium ascorbyl phosphate. We showed that sodium ascorbyl phosphate was stable in both types of microemulsion with no significant influence of its location in the carrier system. To obtain liquid microemulsions appropriate for topical application, their viscosity was increased by adding thickening agents. On the basis of rheological characterization, 4.00% (m/m) colloidal silica was chosen as a suitable thickening agent for w/o microemulsions and 0.50% (m/m) xanthan gum for the o/w type. The presence of thickening agent and the location of sodium ascorbyl phosphate in the microemulsion influenced the in vitro drug release profiles. When incorporated in the internal aqueous phase, sustained release profiles were observed. This study confirmed microemulsions as suitable carrier systems for topical application of sodium ascorbyl phosphate.

Keywords: Sodium ascorbyl phosphate; Microemulsions; Topical application; Stability; Rheology; Thickening agents

1. Introduction

Vitamin C has been used in cosmetic and dermatological products since it has many favorable effects on the skin. As an antioxidant it can scavenge and destroy aggressive oxidizing agents and free radicals that are importantly involved in the processes of skin aging (Colven and Pinnell, 1996; Keller and Fenske, 1998). Although the skin possesses a wide range of interlinked antioxidant defense mechanisms to protect itself from damage by reactive oxygen species (ROS), the capacity of these systems is limited and they can be overwhelmed by excessive exposure to ROS. Supporting the cutaneous antioxidant defense systems with exogenous antioxidants could thus prevent ROS mediated damage in the skin.

Vitamin C also improves the elasticity of the skin and reduces wrinkles by stimulating collagen synthesis (Padh, 1990; Philips et al., 1994). Because of its ability to suppress pigmentation of the skin and decomposition of melanin it can be used as a whitening agent (Kameyama et al., 1996). But it is an extremely unstable compound, and derivatives, like hydrophilic sodium ascorbyl phosphate or lipophilic esters with fatty acids, were therefore synthesized to improve stability (Austria et al., 1997).

Because of its hydrophilic character, sodium ascorbyl phosphate has lower ability to penetrate in the

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skin. It is therefore very important to select a suitable carrier system to deliver it to the site of action in the skin. Microemulsions as colloidal drug delivery systems are preferred because they normally enhance penetration. After application to the skin, components of the microemulsions interact with the intercellular lipids of the skin, resulting in changes of their liquid lamellar structure. This effect facilitates drug transport (Delgrado-Charo et al., 1997; Schmalfuss et al., 1997). Other advantages of microemulsions are their thermodynamic stability, simple technology of preparation, and high solubilizing power, so large amounts of poorly soluble compounds can be incorporated (Terjarla, 1999).

Microemulsions can be used for topical application in place of ointment or creams by modifying their viscosity. They are often very low viscosity Newtonian fluids however, and cannot be applied directly to the skin (Gasco et al., 1991). The usual way to solve this problem is to add a suitable polymer that is capable of modifying the rheological behavior without significant influence on other desirable features of the microemulsion, like stability and large water/oil interface. The selected polymer must be soluble in the continuous phase to display non-covalent intermolecular interactions such as Coulombic, van der Waals, dipole–dipole, hydrophobic and hydrogen bond interactions. Such physical interactions can act cooperatively and lead to the formation of gel microdomains dispersed in a less viscous sol phase, or to a continuous gel network composed of polymer segments belonging to different chains and pervading the whole system. In either case, the system generally displays weak gel properties (Lapasin and Pricl, 1995). Further, the polymers must be biocompatible and show a limited number of interactions with surfactants in order to be used in pharmaceutical microemulsions. Several thickening agents have already been studied (Osman-Gardabbou et al., 2000a,b; Lapasin et al., 2001).

The aim of the present work was to formulate w/o and o/w microemulsions containing sodium ascorbyl phosphate for topical application. We evaluated the stability of the latter in both types of microemulsion and compared it to the stability of ascorbyl palmitate, which is a lipophilic derivative of vitamin C. Additionally, we tried to optimize the rheological behavior of the microemulsion intended for topical use, by adding selected thickening agents and determining their optimal concentration. Finally, we investigated the influence of microemulsion type and the presence of thickening agents on the release profiles of the active ingredient in vitro.

2. Materials and methods

2.1. Materials

Sodium ascorbyl phosphate was provided by BASF (Germany). Its chemical structure is shown in Fig. 1. Ascorbyl palmitate was from Hoffmann La Roche (Switzerland). The microemulsions consisted of the medium chain length 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 the hydrophilic phase. Water was prepared by distillation of reverse osmosis water.

The following thickening agents were used: hydroxypropyl methyl cellulose (HPMC), Methocel E4M and K4M (Colorcon, UK), which differ in the number of methoxyl groups; ethyl cellulose, Ethylcelluose (Aqualon, UK); methyl cellulose, Methocel A15 (Colorcon, UK); sodium alginate, Protanal LF 120M (FMC BioPolymer, USA); xanthan gum (Fluka, Germany); colloidal silica, Aerosil 200 (Degussa, Germany); magnesium stearate (Fluka, Germany) and cetostearyl alcohol, Lanette O (Cognis, Germany).

2.2. Preparation of microemulsions

Sodium ascorbyl phosphate was incorporated in microemulsions at 1.00% (m/m) by dissolving it in water and adding to the mixture of surfactant and cosurfactant (ratio 4:1). Finally, the oil phase was

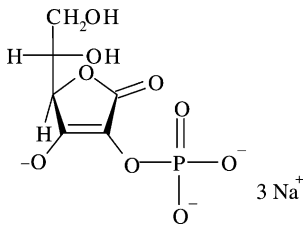

Fig. 1. Chemical structure of sodium ascorbyl phosphate.

Table 1
Composition of w/o and o/w microemulsions (m/m)

Component	w/o (%)	o/w (%)
Mygliol 812	24.75	7.43
Labrasol	47.53	38.02
Plurol oleique	11.88	9.50
Purified water	15.84	45.05

admixed. Microemulsions formed spontaneously after gentle hand mixing. The quantitative compositions of both types of microemulsion are shown in Table 1. Thickening agents were added following procedures described in detail in Section 3.2.

Microemulsions containing 1.00% (m/m) ascorbyl palmitate were also prepared. Ascorbyl palmitate was dissolved in Labrasol, in which it is most soluble, and then the three other components were added (Špiclin and Gašperlin, 1999).

2.3. Stability of sodium ascorbyl phosphate

The stability of sodium ascorbyl phosphate was determined in samples kept at room temperature ($22 \pm 1\,^{\circ}C$) in the dark over a period of 2 months. The amount of non-degraded active ingredient was determined quantitatively by HPLC. The stationary phase was a 250 mm × 4 mm i.d. column packed with 100 μm Nucleosil NH_2, the mobile phase acetonitrile–0.3 M phosphate buffer pH 4 (40:60), the flow rate 0.8 ml min^{-1}, injection volume 20 μl and UV detection was at 258 nm. Before injection, 100 μl of microemulsion were diluted 1:100 (v/v) with tetrahydrofuran-0.3 M phosphate buffer pH 4 (7:3) and then further diluted with 0.3 M phosphate buffer pH 4 to a final 1:1000 (v/v) dilution.

2.4. Stability of ascorbyl palmitate

The stability of ascorbyl palmitate was determined by HPLC in samples kept at room temperature ($22 \pm 1\,^{\circ}C$) in the dark for 4 weeks. The stationary phase was a 120 mm × 4 mm i.d. 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 was at 254 nm. Before injection, 100 μl of microemulsion were diluted 1:100 (v/v) with methanol.

2.5. Rheological studies

Rheological characterization was performed using a controlled stress rheometer (Haake RS 150, ThermoHaake, Germany), equipped with a cone and plate sensor system (C 60/4). Tests were carried out under destructive and non-destructive shear conditions at $20 \pm 1\,^{\circ}C$. Flow curves were measured by stress sweep tests. Under non-destructive shear conditions of oscillatory shear the linear viscoelastic regime was determined at a frequency of 1 Hz. The frequency dependences of dynamic moduli (storage $-G'$ and loss modulus $-G''$) were measured under the condition of linear viscoelastic response.

2.6. In vitro release studies of sodium ascorbyl phosphate

The amount of sodium ascorbyl phosphate and its release profiles were determined in vitro using a flow-through diffusion cell (Sartorius-membranfilter GmbH, Gottingen, Germany) and a hydrophilic cellulose membrane. The acceptor medium was phosphate buffer pH 7.4 at $37 \pm 0.5\,^{\circ}C$. The samples were taken at predetermined time intervals over 8 h and assayed by UV spectrophotometry at 258 nm (UV Spectrophotometer 8453, Hewlett Packard, Germany).

3. Results and discussion

3.1. Stability of sodium ascorbyl phosphate in microemulsions

The quantitative composition of microemulsions, shown in Table 1, was selected on the basis of the pseudoternary phase diagram constructed previously from Miglyol, Labrasol, Plurol oleique and water (Gašperlin and Špiclin, 2001). The chosen microemulsions were of both types. Because of its hydrophilic character sodium ascorbyl phosphate was located in the external aqueous phase of o/w and in the internal phase of w/o microemulsions. Its stability was tested in both types of microemulsions, stored in the dark at 1.00% (m/m) initial concentration. As expected, it was stable in both microemulsions with no significant influence of the location in the carrier system (Student 's t-test at $\alpha = 0.05$). After 2 months, more than

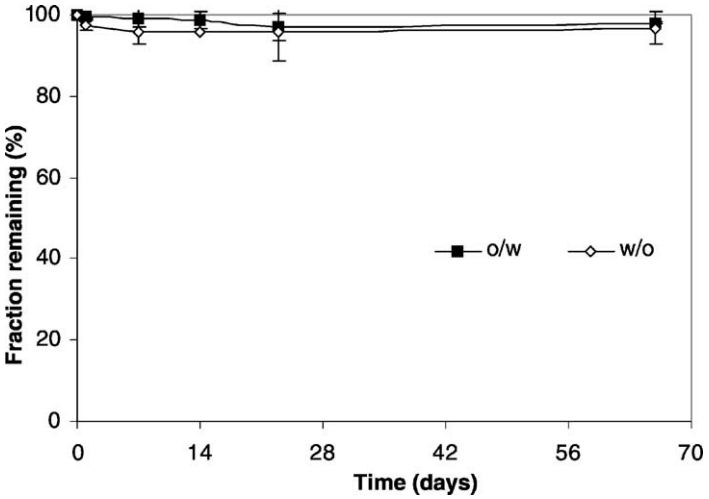

Fig. 2. Stability of sodium ascorbyl phosphate in o/w and w/o microemulsions.

95% of non-degraded compound remained in both microemulsions (Fig. 2). According to literature data and producer specification, ascorbyl phosphate salts are among the most stable ascorbic acid derivatives. High stability is the 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 against oxidation, so ascorbyl phosphate salts cannot act as an antioxidant agents to stabilize formulations (Austria et al., 1997). In order to achieve an anti-oxidizing function it has to be converted into free vitamin C by enzymes present in the skin, which thus supports cutaneous antioxidant systems.

The stability of the hydrophilic ascorbic acid derivative was compared to that of a lipophilic derivative, ascorbyl palmitate, tested in the same microemulsions and at the same concentrations. It was incorporated in the lipophilic phases of microemulsions. In ascorbyl palmitate the enediol system of the molecule is not protected because palmitic acid is introduced in the sixth position of the cyclic ring. The fractions of non-degraded ascorbyl palmitate and sodium ascorbyl phosphate remaining after 4 weeks of storage are shown in Table 2. In both carrier systems the stability of ascorbyl palmitate was much lower than that of sodium ascorbyl phosphate. However, ascorbyl palmitate was significantly more stable in the w/o microemulsion, as described in detail in our earlier publication (Špiclin et al., 2001).

These results confirm the stability of sodium ascorbyl phosphate in microemulsions and support its possible use as an active ingredient with an antioxidant action in the skin.

3.2. Thickening of microemulsions

The very low viscosity often exhibited by microemulsions is inappropriate for topical use. The viscosity can be increased by adding thickening agents, which also change the appearance of the system, usually improve stability and influence drug release. Because of different character of external phase of the selected microemulsions (oil for w/o type and water for o/w type) different thickening agents had to be used.

Table 2
Fractions of non-degraded ascorbyl palmitate and sodium ascorbyl phosphate remaining after 4 weeks storage at the same initial concentration

Active ingredient	Carrier system	Fractions of non-degraded active ingredient (%)
Ascorbyl palmitate	w/o microemulsion	19.02 ± 0.50
	o/w microemulsion	12.83 ± 1.03
Sodium ascorbyl phosphate	w/o microemulsion	96.48 ± 3.24
	o/w microemulsion	97.53 ± 0.37

Table 3
Thickening agents tested for w/o and o/w microemulsions

Microemulsion type	Thickening agent	Concentration	Observed state after 24 h
W/O	Magnesium stearate	3.00% (m/m)	Stable macroemulsion
	Colloidal silica	3.00% (m/m)	Microemulsion
	Cetostearyl alcohol	6.00% (m/m)	Flocculation
O/W	Ethyl cellulose	3.00% (m/m)	Sedimentation
	Sodium alginate	3.00% (m/m)	Phase separation
	Methyl cellulose	3.00% (m/m)	Phase separation
	HPMC K4M	3.00% (m/m)	Phase separation
	HPMC E4M	3.00% (m/m)	Phase separation
	Xanthan gum	3.00% (m/m)	Stable opalescent system

As thickeners for w/o microemulsions magnesium stearate, colloidal silica and cetostearyl alcohol were selected (Table 3). They were added in 3.00% (m/m) concentration in already prepared microemulsions. Systems were mixed with a magnetic stirrer until the equal distribution was attained. They were checked visually after 24 h for physical stability and on that basis colloidal silica was selected. The obtained microemulsion remained transparent with increased viscosity.

For o/w microemulsions a wider range of thickening agents were tested (Table 3). Only xanthan gum was found appropriate, although microemulsions were not transparent. In order to improve the thickening process for o/w systems the procedure was modified. A procedure in which thickening agent was admixed with oil, surfactant and cosurfactant before adding water was better than addition of thickening agent to an already prepared system. Using the last procedure, stable o/w microemulsions with xanthan gum were formed.

3.3. The influence of thickening agent on the viscosity of microemulsions

Thickened and non-thickened microemulsions were characterized by rheology under destructive conditions by applying stress sweep tests and non-destructive shear conditions of oscillatory shear. Non-thickened microemulsions of both types are low viscosity

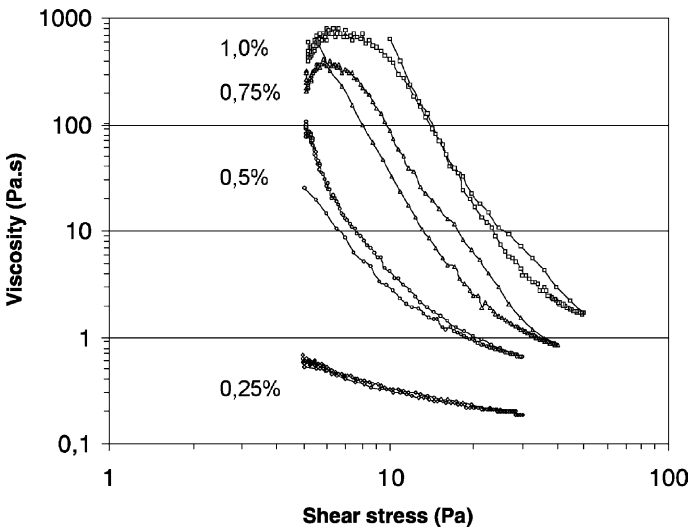

Fig. 3. Flow curves of o/w microemulsions thickened with xanthan gum.

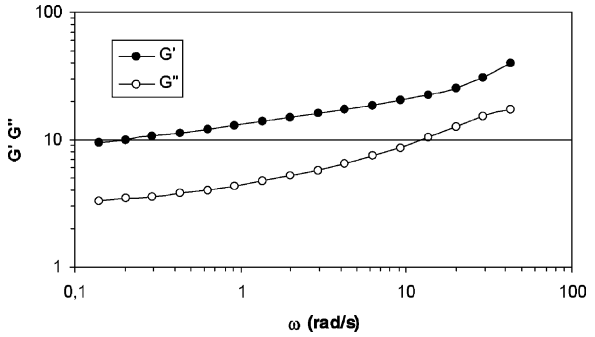

Fig. 4. Frequency dependence of G' and G'' for o/w microemulsion thickened with 0.50% (m/m) of xanthan gum, at constant strain amplitude $\gamma = 5\%$.

Newtonian fluids with viscosity at 20 °C being lower than 1 Pa s.

When o/w microemulsions were thickened with xanthan gum the concentration ranged between 0.25 and 1.00% (m/m). As is shown in Fig. 3, the viscosity considerably increased with increasing concentration of xanthan gum, especially in the low shear stress region. At the same time the flow curves becoming more shear stress dependant. The non-destructive shear measurements were performed in the region of linear viscoelastic response, which was obtained by deformations less than 15–20% of the shear strain amplitude, depending on the polymer concentration. Frequency dependence of the dynamic moduli for all o/w microemulsions thickened with xanthan gum showed the elastic contribution (G') prevailed over the viscous one (G'') over the whole measured frequency range. Fig. 4 demonstrates frequency dependence of microemulsion thickened with 1.00% (m/m) of xanthan gum, where the elastic modulus dominated significantly. According to the rheological behaviour of o/w microemulsions, it can be concluded that the system is transformed from being a polymeric solution (at 0.25% of xanthan gum in the dispersion, with no significant interaction between xanthan molecules) through structured systems (0.5–0.75%) and further to weak-gel behaviour (at 1.00%), which was attributed to physical entanglement of polymer chains.

In order to obtain similar viscosities for the opposite type of microemulsions, samples were thickened with colloidal silica within the concentration range from 1.00 to 4.00% (m/m). From flow curves, shown in Fig. 5, it is evident that interactions among the silica particles, which could be responsible for the structure formation or even for gel-like behaviour, become important only at higher concentrations of the thickener. Viscosity of the systems containing 1.00 and 2.00% (m/m) colloidal silica increased with the increasing silica content, but it was only slightly shear-dependent.

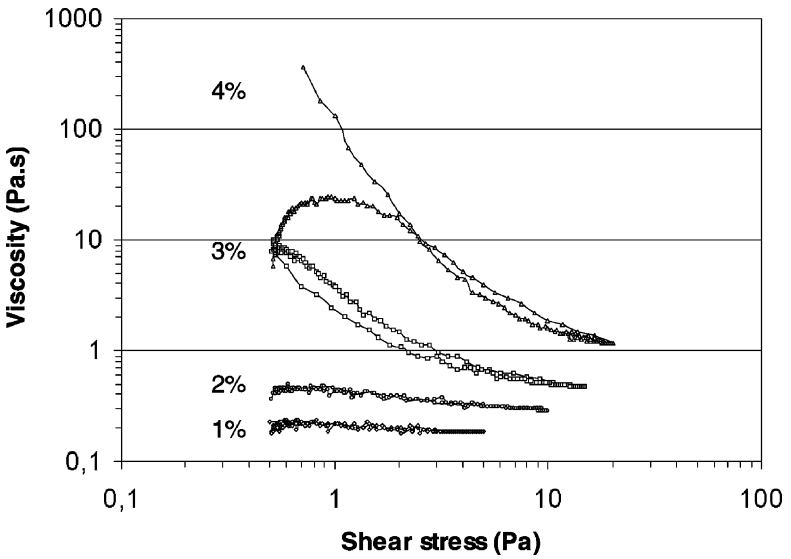

Fig. 5. Flow curves of w/o microemulsions thickened with colloidal silica.

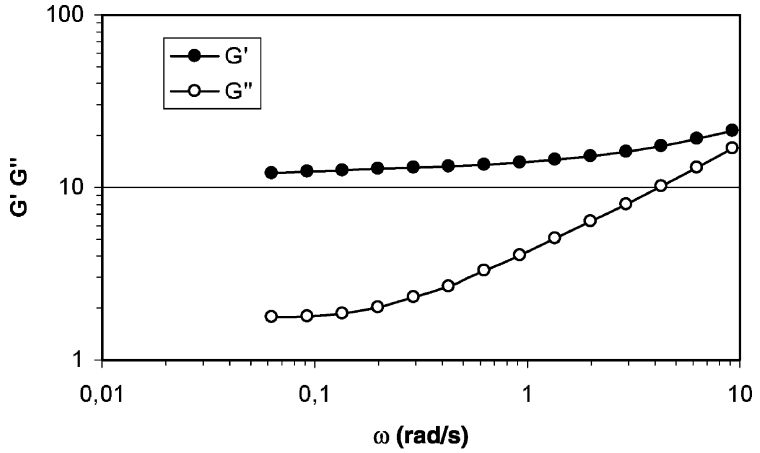

Fig. 6. Frequency dependence of G' and G'' for w/o microemulsion thickened with 4.00% (m/m) of Aerosil, at constant strain amplitude $\gamma = 0.4\%$.

Pronounced shear-thinning behaviour was observed when the concentration of thickener was higher than 3.00% (m/m). The rheological tests under oscillatory shear conditions to obtain linear viscoelastic regime showed that the upper limit of linear viscoelastic response was shifted toward lower values of strain amplitude (12–1%) and it was more influenced by the silica concentration, with respect to o/w thickened microemulsions. Frequency sweep tests showed that at low concentrations of colloidal silica (1.00–2.00% (m/m)) the viscous contribution prevailed the elastic one over whole examined frequency range, whereas for the system at the highest silica concentration 4.00% being presented in Fig. 6, the elastic contribution became predominant throughout whole frequency range. From the rheological investigation one can arrive to a conclusion that gel-like behaviour of w/o microemulsions was achieved when the concentration of colloidal silica was above 3.00% (m/m).

3.4. Release of sodium ascorbyl phosphate

Thickened microemulsions with approximately the same viscosity were selected for release studies. They

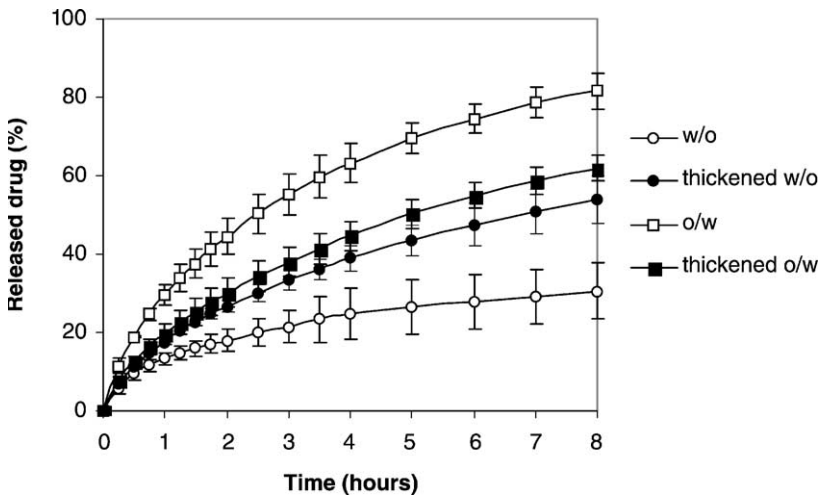

Fig. 7. The release profiles of sodium ascorbyl phosphate from o/w and w/o microemulsion.

Table 4
Pearson coefficients for the cases of zero-order, first-order and Higuchi kinetics

Sample	Zero-order[a]	First-order[b]	Higuchi[c]
Non-thickened w/o microemulsion	0.9478	0.8522	**0.9912**
Thickened w/o microemulsion	0.9738	0.8767	**0.9993**
Non-thickened o/w microemulsion	0.9561	0.8530	**0.9945**
Thickened o/w microemulsion	0.9746	0.8775	**0.9993**

[a]Represents the extent of a linear relationship between Q_t and t; [b]represents the extent of a linear relationship between $\ln Q_t$ and t; [c]represents the extent of a linear relationship between Q_t and $\sqrt{t}$; where Q_t is a percentage of released sodium ascorbyl phosphate.

were w/o microemulsion thickened with 4.00% (m/m) colloidal silica and o/w microemulsion with 0.50% (m/m) xanthan gum. The release profiles are shown in Fig. 7. From both thickened and non-thickened w/o systems, less sodium ascorbyl phosphate was released than from o/w systems, indicating sustained release behavior of w/o microemulsion. The external oil phase is apparently a barrier for the diffusion of a hydrophilic, freely soluble compound. Larger amounts of released sodium ascorbyl phosphate from o/w systems are the consequence of its deposition in the external phase and consequently higher diffusion rate. The addition of xanthan gum decreased the amount of released compound due to the increased viscosity of the system, which influenced the rate of drug diffusion. The addition of colloidal silica led to the opposite effect. The amount of released sodium ascorbyl phosphate was higher in the case of thickened microemulsion. One of the possible explanations for such behavior was offered by conductivity measurements on thickened and non-thickened w/o microemulsions. The specific conductivity of the dispersion system with colloidal silica in the outer phase was higher than that of the non-thickened system (22.59 μS/cm versus 18.74 μS/cm). We assume that colloidal silica modified the physicochemical characteristics of the external phase and hence the diffusion of highly hydrophilic sodium ascorbyl phosphate from the internal through the external phase of the microemulsion.

The release profiles were also evaluated by fitting the experimental data to different order kinetic equations. The data were transformed for linear regression analysis for zero-order, first-order and Higuchi kinetics—the Pearson values are listed in Table 4. In all cases best fits were found with Higuchi kinetics, based on the equation:

$$Q = \sqrt{D^* t^* c_s^* (2c_o - c_s)},$$

where Q, is the amount or percentage per unit area absorbed at time t, c_o, the original concentration of the drug in the vehicle, and D, the diffusivity of the drug in the vehicle. Based on this equation we conclude that the rate-determining step for sodium ascorbyl phosphate release from microemulsions is transport within the carrier system (Kalia and Guy, 2001).

4. Conclusion

Sodium ascorbyl phosphate was incorporated in two microemulsions differing only in quantitative composition and consequently in microemulsion type. Both microemulsions were thickened to obtain a viscosity appropriate for dermal application. On the basis of rheological characterization 4.00% (m/m) colloidal silica was chosen for w/o and 0.50% (m/m) xanthan gum for o/w microemulsions. The presence of thickening agent and the location of sodium ascorbyl phosphate in the microemulsions significantly influenced its release profiles but had no effect on its stability. These results confirmed microemulsions as suitable carrier systems for topical application of sodium ascorbyl phosphate.

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