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RESEARCH PAPER

Consideration on the Formulation of Benzoyl Peroxide at Ambient Temperature: Choice of Non-polar Solvent and Preparation of Submicron Emulsion Gels

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ABSTRACT

The aim of this study performed at ambient temperature was first to determine the solubility of benzoyl peroxide in various solvents with a large range of polarity. All these solvents can be used in the dermatological field. Then, using the most suitable solvent, a new drug vehicle submicron oil-in-water emulsion was formulated. Correlation between dielectric constant (ε) and drug solubility in various solvents and different binary mixtures was verified. An original ternary diagram with surfactant–co-surfactant/oil/water was performed at low temperature to determine the regions of submicron emulsions. A dramatic change in the magnitude of benzoyl peroxide solubility occurred above a dielectric constant value of about 20. The solubility of this drug can be enhanced by the replacement of polar solvent by a vehicle of lower dielectric constant. A stable submicron emulsion gel was made with cremophor EL, glycerol, caprilic–capric triglycerides, and water in the proportion of 20–20/35/25, respectively; 1.5% benzoyl peroxide was also added. This submicron emulsion vehicle consisted of oil droplets, with a mean diameter of approximately 100–150 nm, dispersed in a continuous water phase. These studies confirm the potential of benzoyl peroxide incorporation into submicron emulsion gel and the stability of this formulation.

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INTRODUCTION

Benzoyl peroxide (BP) is widely used for its antimicrobial anti-inflammatory and keratolytic properties in topical treatment of juvenile acne and rosacea. This drug is poorly soluble in many pharmaceutical solvents and practically insoluble in water. Benzoyl peroxide is available as cream, lotion, or gel at concentrations of 2.5% to 10%, and the base of most formulations is a carbomer 940 gel with BP dispersion.[1] Benzoyl peroxide can also be dispersed in an aqueous medium and stabilized by the presence of glycerol.

In a first step, the solubilization of BP was characterized via the dielectric constant. The dielectric constant has long been used as a significant parameter for explaining solubility data of poorly soluble drugs. For any solute, the solubility shows a maximum at a certain value of the dielectric constant of the solvent.[2,3] For non-electrolytes, the solute is more soluble in solvent systems with low dielectric constants. According to this theory, every solute shows a maximum solubility in any given solvent system, at more or less specific dielectric constant.[4] In the pharmaceutical field, the most commonly used measures of polarity are dielectric constant (ε), solubility, and surface tension. It is recognized that the dielectric constant is not the best nor a unique measure of solvent polarity, but one of the advantages of this parameter is that its value is usually known for most pharmaceutical solvents.[5–8]

The purpose of this work was to study an alternative formulation such as an oil-in-water submicron emulsion where the BP was dissolved in the oily phase. Submicron emulsions are a priori interesting candidates for delivery of drugs to the skin.[9] Submicron emulsion gels (emulsions which contain a dispersed phase with mean droplet diameter largely under 1 μm) typically have greater stability to physical degradation than do coarse emulsions. In this final formulation, it was desirable that the BP be incorporated at 1.5%. The selected mixture must also contain non-irritating solvents for the skin and solubilize the drug at adequate concentrations. The major difficulty in BP formulation is the extreme reactivity of this drug and its thermal degradation in solution; for example, at 40°C benzoyl peroxide is rapidly destroyed. Recently, Vermeulen et al.[10] have described the influence of storage temperature and non-active ingredients on the stability of benzoyl peroxide and erythromycin in topical gel preparations for extempore compounding. Some solvents are moreover known to produce an adverse effect on stability with time during the storage of benzoyl peroxide, for example ethanol,[11] polyethylene,[12] and polyethylene glycol (PEG) 400.[13] A summary of this review demonstrated that the stability of BP in pharmaceutical formulations is strongly influenced by the makeup of the preparation. In view of these difficulties, it seems essential to formulate BP by simple gentle stirring for a short time at ambient temperature (25°C).

This work was initiated to fill this void, the first step being to determine a pharmaceutically acceptable solvent. The solvent selected must, in the second step, yield a stable submicron emulsion.

MATERIALS AND METHODS

Chemicals and Reagents

Benzoyl peroxide (purity >97%) was purchased from Fluka (Saint Quentin Fallavier, France); PEG-35 castor oil (Cremophor EL) was obtained from BASF (Ludwigstafen, Germany). Different vehicles: apricot kernel oil PEG-6 esters (Labrafil M 1944 CS, Gattefosse (Lyon, France)), butanol-1 (RP normapur Prolabo (Fontenay sous Bois, France)), propyl alcohol (RPE, Carlo Erba (Nanterre, France)), caprilic–capric triglycerides—a medium chain triglyceride (Miglyol 812, Hüls (Marl, Germany)), ethoxydiglycol (Transcutol, Gattefosse), ethyl alcohol 100% (RPE, Carlo Erba), glycerin (Prolabo), PEG-8 caprilic–capric glyceride (Labrasol, Gattefosse), propylene glycol (Prolabo), polyethylene glycol 400 (Sigma (Saint Quentin Fallavier, France)), tristearin PEG-6 esters (Labrafil isostearique, Gattefosse), and sterile water (Agettant (Lyon, France)).

Materials

A Uvikon 922 spectrophotometer (Kontron Instrument) was used to record the absorption spec-

trum of benzoyl peroxide in ethyl alcohol (continuous agitator, Astra). Formulations were performed at $24 \pm 1^{\circ}C$ with a homogenizer at 400 rpm (Turbotest 33/300, Rayneri). Measurements of droplet sizes were made using a SemaTech photogognio-diffusiometer (SEM-633) operating at 632.8 nm and with a He–Ne laser as the source of incident light. This instrument was combined with a correlator SEM (RTG) using 12 channels, log–log corresponding to 4096 channels. The cylindrical scattering cells were immersed in a thermostatted bath ($25 \pm 1^{\circ}C$) of index-matching liquid (toluene). Data in the homodyne mode were collected at a scattering angle of 90°.

Solubility Determination

Benzoyl peroxide solubility in different solvents was determined in triplicate at $25 \pm 1^{\circ}C$. A quantity of BP (3 g) far in excess of the intrinsic solubility was placed in a 60-mL capped glass vial. To each vial was added 12 g of appropriate solvent. The vials were then stirred at $25 \pm 1^{\circ}C$ for 24 hr, to ensure equilibrium solubilization. Samples of saturated solutions were centrifuged for 15 min at 10,000 rpm and filtered (if necessary) through filter paper. The loss of compound caused by adsorption to filter material was minimized by choosing a sufficiently high foreum. The solutions were then suitably diluted with absolute ethyl alcohol for measurement. The concentration of BP in each solvent was determined spectrophotometrically at 234 nm.

Preparation of Submicron Emulsion Gel

A phase diagram was drawn up with the following constituents: a mixture of cremophor EL and glycerin (50/50, w/w) and caprilic–capric triglycerides was used as oily phase, with sterile water as aqueous phase. Cremophor EL ethylene oxide derivative of castor oil (mainly ricinoleic acid) is commonly used as a non-ionic emulgent and solubilizer for pharmaceutical preparations. It is a light yellow, limpid, oily liquid. The diagram was realized point by point. The caprilic–capric triglycerides and the mixture of cremophor EL with glycerin were mixed in a homogenizer. The water was then added drop by drop. The formulation temperature was $25 \pm 1^{\circ}C$, under agitation (5 min).

Stability of Submicron Emulsion

Three stability methods were performed with two accelerated tests. The first accelerated test concerned stability at elevated temperatures (7 days at $50 \pm 1^{\circ}C$) and the second concerned stability under centrifugation (10 min at 5000 rpm). The last test included long-term stability at $25 \pm 1^{\circ}C$.

Rheological Studies

In order to show the flow behavior of emulsion a D/τ [shear rate (sec^{-1})/shear stress (Pa)] diagram was drawn with a Rheomat 30 (Contrave) with these conditions: measuring system no. 25, torque range between 15 and 30, 2 for sensibility, and a constant temperature of $25 \pm 1^{\circ}C$. To quantify the rheology of fluids, we use a model usually attributed to Oswald—the power law fluid model.[14] This can be written as: $\tau = KD^n$, where n is the flow behavior index and K is the consistency index.

RESULTS AND DISCUSSION

Solubility

This step was to examine the solubility of BP as a function of the nature of the solvent. To this end, the BP solubility was measured in solvents covering a wide range of physicochemical properties. Before these studies, a scan ($\lambda = 200$–350 nm) of BP was run on the spectrophotometer to ascertain the wavelength of maximum absorption (234 nm) in ethyl alcohol. Linearity over the range 1–10 mg L^{-1} had first to be confirmed.[15] The best-fit equation was $y = 0.0868x + 0.000719$, where y is the peak area and x is milligrams per liter of BP [with $r^2 = 0.998$, a statistically significant relationship between peak area and BP concentration was found; p-value <0.0001 and p-value for the lack-of-fit test in the analysis of variance (ANOVA) table 0.37].

The solubility of BP was first determined at 25°C in 12 pure solvents of known dielectric constant, with the aim of scanning the dielectric constant spectrum for maximum solubility. Nine mixtures of miscible solvents were also tested. Values for a number of binary blends have been reported,[16,17] but they can also easily be estimated. In a binary system, for two pure liquids 1 and 2, the dielectric constant of a mixture ($\varepsilon_{mixture}$) can be estimated via a weight-averaging formula:[18]

$$\varepsilon_{\text{mixture}} = x_1\varepsilon_1 + x_2\varepsilon_2 \quad (1)$$

where ε_1 and ε_2 correspond respectively to the dielectric constant of liquid 1 and liquid 2 and x_1 and x_2 should be a volume or a weight fraction of these liquids.

The solubility values of benzoyl peroxide obtained in this work appear in Fig. 1. As many as five solvents and five mixtures of solvents afford a BP solubility greater than $40\,\text{mg}\,\text{g}^{-1}$, and for three of them the solubility exceeded $60\,\text{mg}\,\text{g}^{-1}$. Benzoyl peroxide dissolving solvents tend to pass through a maximum for a range of ε covering 5–15. The same trend was observed with solvent mixtures. Even the dielectric constant method is not universally applicable: it was shown to be predictive with the mixture of solvent used in each case. We can conclude that a narrow solubility peak was found for dielectric constants between 5 and 15. This tendency is particularly well illustrated in Fig. 1, where the solubility values are plotted against the dielectric constants for the various solvents. The two curves obtained with mixture and pure solvents are superimposable. These data are in good agreement with the discussed relationship between dielectric constant and the solubility of the solvent. On the other hand, experimentally, the solubility in water was below the detection level of this method ($<0.01\,\text{mg}\,\text{L}^{-1}$). Benzoyl peroxide is practically insoluble in polar solvents with an ε value greater than 30. However, the solubility of BP in a novel solvent or a novel mixture of solvents can easily be esti-

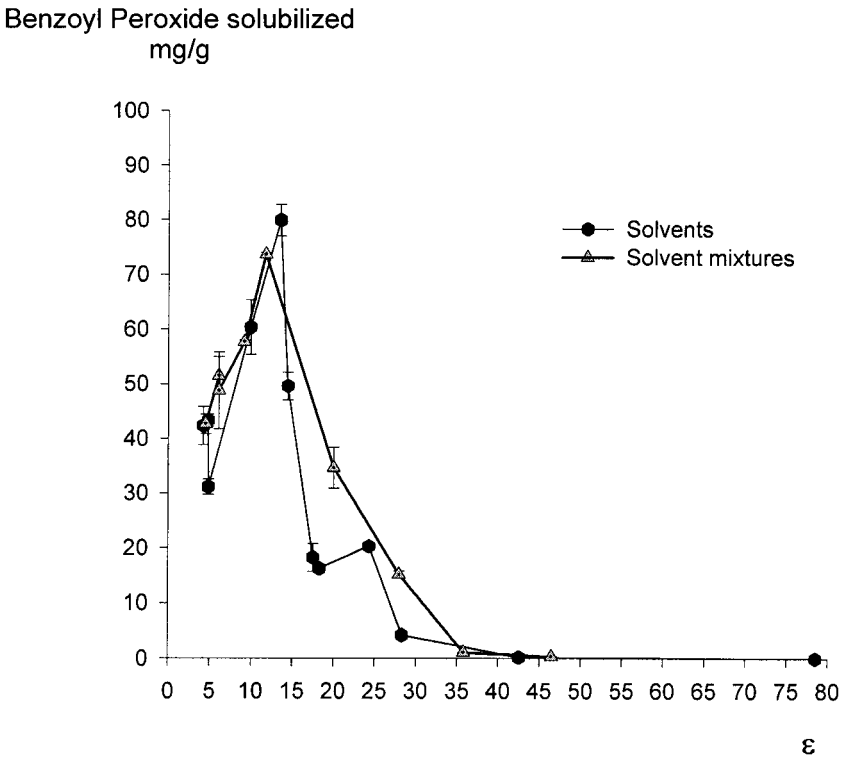

Figure 1. The solubility of benzoyl peroxide ($\text{mg}\,\text{g}^{-1}$) vs. dielectric constant (ε) of pure solvent and solvent mixtures. All data are for 25°C. Values of ε obtained from Ref. 5: apricot kernel oil PEG-6 esters (4.21), capric–caprilic triglycerides (4.78), tristearin PEG-6 esters (4.83), PEG-8 caprilic–capric glycerides (10.52), ethoxydiglycol (13.5). Values of ε obtained from Ref. 13: PEG-400 (14.4), ethanol (24.9), propylene glycol (29). Values of ε obtained from Ref. 7: butanol-1 (17.5), propanol-2 (18.3), glycerol (42.5), water (78). Estimated values of ε for solvent mixtures using Eq. (1): apricot kernel oil PEG-6 esters/capric–caprilic triglycerides (0.5/0.5, w/w) (4.49), apricot kernel oil PEG-6 esters/ethoxydiglycol (0.8/0.2, w/w) (6.07), capric–caprilic triglycerides/ethoxydiglycol (0.85/0.15, w/w) (6.09), capric–caprilic triglycerides/ethoxydiglycol (0.5/0.5, w/w) (9.14), ethoxydiglycol/PEG-8 caprilic–capric glyceride (0.5/0.5, w/w) (11.70), ethanol/ethoxydiglycol (0.6/0.4, w/w) (19.98), ethanol/glycerol (0.8/0.2, w/w) (27.94), PEG 400/water (0.66/0.33, w/w) (35.78), PEG-400/water (0.5/0.5, w/w) (46.47).

mated if its dielectric constant and solubility data in similar solvents are known.

Based on these arguments, it is believed that highly-polar solvents are not an attractive proposition. In all cases mixtures of solvents with water increased the ε, and BP solubility can be lowered dramatically simply by raising the water content. The ability of solvents to solubilize BP appears to be directly related to the non-polarity of the solvent. This capacity suggests that caprilic–capric triglycerides are a good candidate solvent, and with this an oily phase emulsion could be prepared. Another advantage is the non-miscibility of this oil component with water, so the dielectric component cannot increase and diminish the benzoyl peroxide solubility. Aungst et al.[19] have also demonstrated drug solubilization in the vehicle, increased partitioning, solvent penetration, and barrier disruption, each of which can contribute to increased skin permeation rates.

Submicron Emulsion Gels

The stability of BP necessitates formulation at ambient temperature and systems with particle sizes in the submicron range. With this in mind, the diagram method is a useful tool to carry out a systematic study of determined emulsion formulations. The existence of submicron emulsion regions was investigated at ambient temperature (25°C) in quaternary systems composed of non-ionic surfactant, co-surfactant, caprilic–capric triglycerides, and sterile water.

The systems were observed first for visual clarity and consistence. The samples were marked as being optically clear or turbid, emulsions or gels, and presenting a stable system. The H_2O/oil/surfactant–co-surfactant phase diagram, illustrated in Fig. 2, shows the phase regions obtained on which zones of interest were identified. In the center of the diagram, we find an interesting domain of submicron emulsions. Three zones were identified, a region of

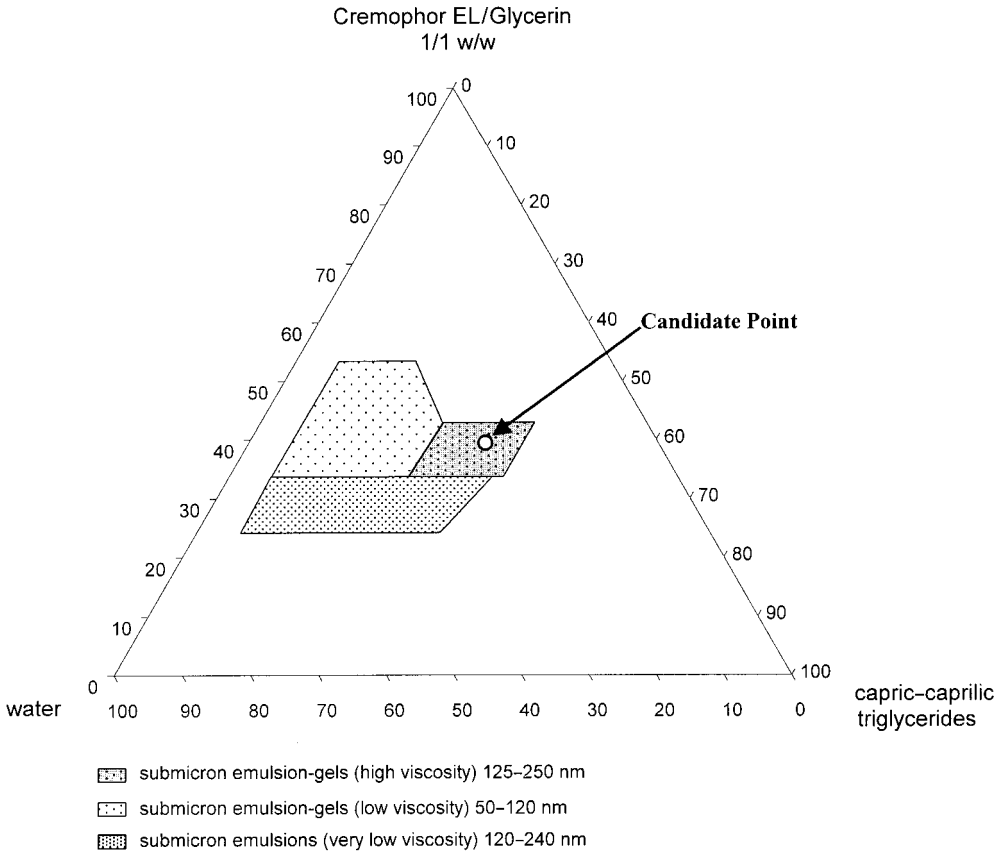

Figure 2. Mass phase diagram of the system water/capric–caprilic triglycerides/cremophor/glycerol. The cremophor/glycerol mass ratio was 1/1. This ternary diagram was performed at 25°C.

oil/water emulsions with a low viscosity and drop size between 120–240 nm, and two restricted areas of emulsion gel. In the first area, because of their extremely small drop size, these mini-emulsions were often translucent, viscous,[20] and more stable. The drop size of these emulsions was in the order of 50–125 nm. They were not microemulsions because they were not thermodynamically stable and could be diluted with their external phase. The last region was also an emulsion gel but more viscous and with a drop size between 125–240 nm. This limited zone of submicron emulsion gel allowed us to select a formulation with a weighty part of oil. The candidate point selected was composed of 25/40/35 water/surfactants/oil. This formulation was the most stable, and with 35% capric–caprilic triglycerides an emulsion with 1.5% BP could be prepared. The two candidate points were formulated in triplicate. From a diffusion viewpoint, the solubility of the drug in the vehicle should be maintained as near to saturation as possible.[21] In caprilic–capric triglycerides we used BP to saturation, $43\,mg\,g^{-1}$, which corresponds to an emulsion formulation at 1.5%.

Submicron emulsion gels obtained in this way were characterized by their particle size distribution, one of the most important characteristics of an emulsion. The photon correlation spectroscopy (PCS) method is considered the most appropriate for studying droplets $<1\,\mu m$, in this work the selected candidate points. Appropriately diluted samples (2 mg in 5 g sterile water) were subjected to PCS (in duplicate). For each emulsion gel we obtained the probability density [$P(D)$] and the mean diameter of the population of particles (Fig. 3). A non-linear regression with Gauss–Newton method was used to estimate the parameters (two analyses of three replicates), and data are reported in Table 1. In the international standard, the two parameters describing particle size distribution, i.e., the average PCS

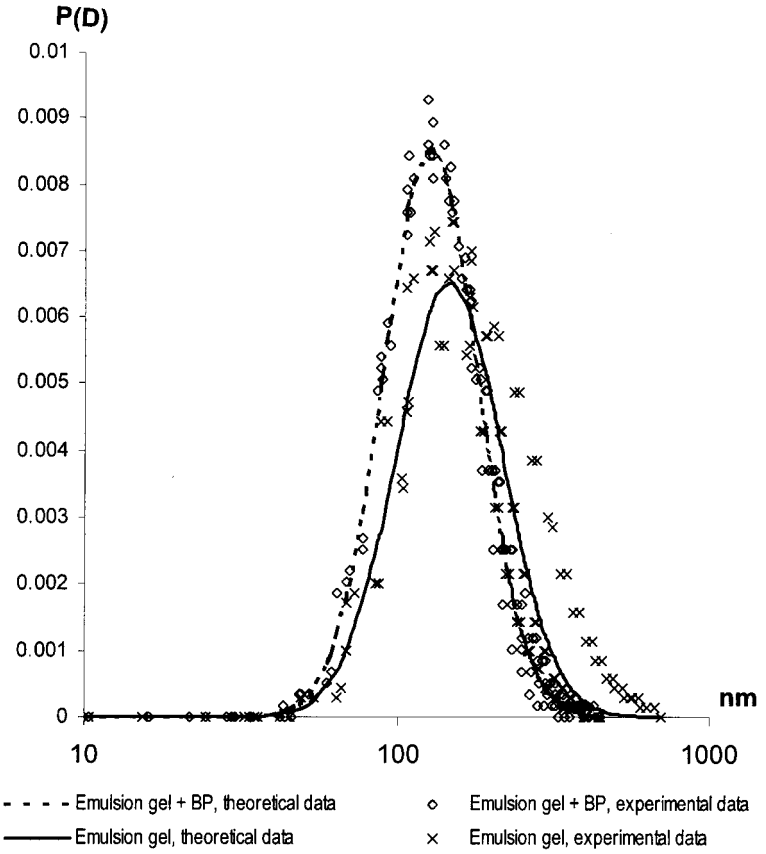

Figure 3. Experimental data and curves obtained by non-linear regression, each formulation was performed in triplicate and analyzed in duplicate ($n = 6$).

Table 1

PCS Characteristics of Submicron Emulsion Gels and Latex (90 nm and 497 nm)

References	Mean Diameter (nm)	Dispersion (nm)	PI
Emulsion gel	145.59	74.13	0.16
Emulsion gel+BP	126.17	54.46	0.13
Latex 90	90.16	3.99	0.002
Latex 497	497.74	186.16	0.10

Table 2

Power-Law Parameters Obtained by Regression of Logarithm of τ on Log D and Regression Coefficients

References	r^2	K (S_K)	n (S_n)
Emulsion gel	0.99	4.78	0.567
		1.05	0.022
Emulsion gel+BP	0.97	4.29	0.574
		1.09	0.019

mean diameter and the polydispersity index (PI), constitute the so-called cumulant method. The PI was calculated according to the International Standard ISO 13321. The PI is a dimensionless measure of the broadness of the size distribution. Measurement of the definite diameter latex (90 nm) following the same protocol gave us a diameter of 90.16 nm (with a dispersion of 3.99 and a PI of 0.002). It should be noted that the mean diameters of the emulsion gels with BP were statistically significantly different from the distribution of the free drug emulsion gels. In our case, the size distribution showed a minor decrease of all PCS parameters. These results indicate a better stability of BP emulsion gels, since emulsion instability is generally characterized by an increase in droplet size. This interesting technique has clearly shown a population of dispersed oil droplets with a narrow range distribution, 100–150 nm, for an emulsion gel prepared under the experimental conditions described above.

The flow behavior of these submicron emulsion gels was characterized and the regression coefficients are reported in Table 2. The two curves obtained are very similar and the two coefficients of determination, $r^2 = 0.99$ and 0.97, show that the power law model is a suitable fit for the experimental data of examined submicron emulsions. In two cases, the flow behavior index is near 0.5, and this corresponds to a strong shear thinning behavior. The second constant, the consistency index, is also very similar for the two formulations. By comparing these power-law parameters, addition of PB in this formulation has no significant effect on rheological properties.

These formulations were stable with two accelerated tests used. The first concerned stability at elevated temperatures (7 days at 50°C) and the second concerned stability under centrifugation (10 min at 5000 rpm). They were also macroscopically stable for 8 months at 25 ± 1°C.

CONCLUSION

The major objective of this study was to determine the solubility of BP in several solvents. However, the solubility of BP in various solvents had already been studied by different authors. So, the solvents used here were focused in the dermatological field. Submicron emulsions were performed with low energy, room temperature, and gentle agitation to prevent in particular thermal decomposition of BP.

A relationship between solubility of benzoyl peroxide in solvent, binary mixed solvent, and dielectric constant was well demonstrated. In this work we found that the drug solubility was enhanced using solvents (pure or mixture) with dielectric constants between 5 and 15. The formation of submicron emulsion gels in ternary surfactant–co-surfactant/oil/water mixtures allowed the formulation of oil-in-water emulsions with monodispersed droplets <200 nm in size. The decomposition of BP is complex and influenced by many factors, especially the temperature. This methodology realized at room temperature was able to prevent the thermal decomposition of BP. Submicron emulsions are novel vehicles of oil-in-water type dispersion and can be used as drug carriers, as has been suggested or reported recently by several authors.[22–25] Advantages may be taken from such favorable submicron emulsion properties.

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