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Benzoyl Peroxide Solubility and Stability in Hydric Solvents

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Saturated solubility and reaction rate constants for the decomposition of benzoyl peroxide in solution and suspension were determined for use in formulation development. The solvents studied included ethanol, propylene glycol, and cosolvent mixtures of PEG 400 and water. The solubility of benzoyl peroxide was inversely related to the solvent polarity, with greater solubility occurring with semipolar solvents. The stability of benzoyl peroxide in solution was dependent on the solvent, concentration of benzoyl peroxide, and temperature. The compound was least stable in PEG 400. Stability was improved when water was added to PEG 400. Similar solvent effects were observed in suspension. In benzoyl peroxide suspensions of PEG 400 and PEG 400/water blends, benzoyl peroxide stability was dependent on solubility, with improved stability occurring in blends where the benzoyl peroxide was least soluble. Thus, solution formulations of benzoyl peroxide in pharmaceutically acceptable solvents are unlikely to show good stability; however, suspension formulations should be reasonably stable if the vehicle is selected to provide low benzoyl peroxide solubility.

KEY WORDS: benzoyl peroxide; free radicals; stability, kinetics; preformulation.

INTRODUCTION

Benzoyl peroxide (BP) is commonly used in topical formulations for the treatment of acne and, more recently, athlete's foot. Benzoyl peroxide is available as a lotion, cream, gel, cleanser, liquid, bar, or mask at concentrations of 2.5, 5.0, or 10% (1). These formulations may contain water, propylene glycol, isopropyl myristate, acetone, or alcohol in the product vehicle. The chemical instability of benzoyl peroxide makes formulating such products difficult.

Benzoyl peroxide is extremely reactive and degrades in solution at low temperatures (<40°C), because of the instability of the O–O bond, which has a bond energy of approximately 30 kcal/mol (2), compared to 83 kcal/mol for a C–C bond. The degradation of benzoyl peroxide in solution proceeds through a free radical mechanism (3–7). The benzoyl peroxide degradation pathway is shown in Scheme I. Benzoyl peroxide degrades thermally to form benzoate-derived radicals, in the initiation step. These benzoate radicals can propagate the reaction by reacting either with benzoyl peroxide or with solvent to form solvent radicals and other benzoate radicals which react with benzoyl peroxide. The number of propagation reactions per initiation reaction determines the chain length. The reaction is terminated when two radicals couple together. Depending upon the steps chosen, such a scheme can lead to a variety of kinetics. A chain involving only peroxide (reactions 1, 2, and 5) introduces a three-halves-order term in the kinetics, whereas chains involving solvent (reactions 1, 3, and 4) give one-half-, first-, or three-halves-order kinetics, depending upon whether termination is by reaction 5, 6, or 7, respectively (2,6,8).

The stability of benzoyl peroxide in pharmaceutical formulations depends in part on the solvents employed (9). Bollinger *et al.* examined the effects of solvents and surfactants in water on the stability of 10% benzoyl peroxide gel formulations (9). The formulations prepared with alcohol (40%) were less stable, with a loss of 50% following 90 days at 40°C, compared to a 20% loss in laureth 4 (6%) and a 10% loss in propylene glycol (5%). There was no measurable loss of benzoyl peroxide in formulations containing acetone (10%).

Limited kinetic data exist regarding the effects of pharmaceutical solvents on the stability of benzoyl peroxide. The objective of this investigation was to determine the saturation solubility of benzoyl peroxide and the rates of degradation, in solution and suspension, of cosolvent mixtures of polyethylene glycol (PEG 400) and polyols. The solvents were selected to represent a wide range of polarity. PEG 400 was chosen because it is noncomedonegenic and less irritating than smaller-chain polyols.

MATERIALS AND METHODS

Chemical and Reagents. Polyethylene glycol 400 (NF grade) was obtained from Rueger Chemical Co. (Irvington, NJ); propylene glycol from Rueger Chemical Co.; acetonitrile (HPLC grade), methylene chloride (HPLC grade), and methanol (HPLC grade) from J. T. Baker (Phillipsburg, NJ); glycerol (ACS grade) and *o*-phosphoric acid (85%, ACS grade) from Fisher Scientific (Fair Lawn, NJ); benzoic acid (NF grade) from Rueger Chemical Co. (Irvington, NJ); ethanol, 200 proof (USP grade), from Quantum Chemical Corporation (Tuscola, IL); benzoyl peroxide (>97% pure) from Aldrich Chemical Co. (Milwaukee, WI); and purified water (USP grade) from Sterling Research Group (Rensselaer, NY).

High-Performance Liquid Chromatography. The HPLC system consisted of a Waters 510 solvent delivery system (Waters Associates, Milford, MA), equipped with a single-wavelength detector (Spectroflow 757 Absorbance Detector, ABI Analytical, Ramsey, NJ), a Waters Maxima 820 data module, and a Waters 712 WISP. Samples were separated on a reverse-phase column, 25 × 0.5 cm (Partisil 10 ODS-3, Whatman, Clifton, NJ). The mobile phase consisted of acetonitrile:water:85% phosphoric acid (700:300:2) at a flow rate of 1 ml/min. The UV detector was fixed at 254 nm. For assay, 25 μl was injected onto the column. Quantification was achieved by creating a linear calibration plot of instrument response (area units) versus concentration of standards (0.5–200 μg/ml). The correlation coefficient of each day's linear calibration plot was, in each case, at least 0.990. Standards and samples were diluted to volume with acetonitrile. Samples were diluted such that sample concentration measured was between 0.5 and 200 μg/ml. Under the above conditions, benzoic acid had a retention time of 3.6 min with a capacity factor of 0.38 and a 7.8-min retention time for benzoyl peroxide with a capacity factor of 7.5.

Determination of the Dielectric Constant (DEC). Mea-

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$$\begin{array}{llcll}
1. & BP & \xrightarrow{k_i} & 2P\bullet & \text{INITIATION} \\
2. & P\bullet + BP & \xrightarrow{k_{p1}} & P\bullet & \\
3. & P\bullet + S & \xrightarrow{k_{2p1}} & S\bullet & \text{PROPAGATION} \\
4. & S\bullet + BP & \xrightarrow{k_{2p2}} & P\bullet & \\
5. & 2P\bullet & \xrightarrow{k_{t1}} & X & \\
6. & P\bullet + S\bullet & \xrightarrow{k_{t2}} & Y & \text{TERMINATION} \\
7. & 2S\bullet & \xrightarrow{k_{t3}} & Z &
\end{array}$$

Scheme I. Mechanism of benzoyl peroxide decomposition, where BP represents peroxide, $P^{\bullet}$ and $S^{\bullet}$ represent unspecified radicals derived from peroxide and solvent, and X, Y, and Z represent unspecified products.

surements were made with an oscillometer (Sargent Chemical Oscillometer Model V, E. H. Sargent and Co., Chicago, IL) at 25°C. The cell constant was calculated to be 6671, derived by measurements with liquids of known dielectric constants: methylene chloride (DEC of 8.93) and water (DEC of 78.5).

Solubility Determinations. An excess of benzoyl peroxide (1.0 g) was added to 10-ml glass culture tubes with Teflon-lined closures containing 5 ml of either ethanol, propylene glycol, glycerol, ethanol/water (1:1), propylene glycol/water (75:25), or PEG 400/propylene glycol (6:4, w/w). These tubes were rotated on a shaker maintained at ambient temperature for 24 hr, centrifuged, and filtered (0.5-μm nylon filter, Spartan-25, Schleicher and Schuell). An aliquot of the filtrate was weighed (approximately 200 mg) and diluted appropriately for HPLC measurement.

In a 125-ml flask containing approximately 100 ml of PEG 400, an excess of benzoyl peroxide (10 g) was added, stirred overnight, centrifuged, and filtered. An aliquot (approximately 200 mg) of the filtrate was diluted appropriately for HPLC measurement. Solubility of benzoyl peroxide in PEG 400/water cosolvent mixtures (10, 20, 30, 40, 50, 60, 70, 80, and 90% PEG 400, w/w) was determined by adding, by weight, a specific amount of PEG 400 filtrate saturated with benzoyl peroxide to a specific weight of water in a 10-ml culture tube such that the total weight was 5.00 g. The tubes were rotated on a shaker for 24 hr, then filtered, and an aliquot was weighed (approximately 200 mg) and diluted appropriately for HPLC measurement.

Preparation of Solution for Stability Studies. The solution stability of benzoyl peroxide was performed in cosolvent mixtures of PEG 400/water (100, 90, 80, and 70% PEG 400, w/w), PEG 400/propylene glycol (6/4, w/w), ethanol, and propylene glycol. The concentrations of benzoyl peroxide (mg/g) in these solvents are presented in Table II. Solutions were transferred to 25-ml glass vials with polypropylene-lined tops and placed at ambient temperature, in darkened stability ovens maintained at 40, 50, and 70°C (±2°C) at ambient relative humidity. At specific time intervals, an aliquot was weighed (approximately 200 mg) and diluted appropriately for HPLC measurement. For stability studies at 70°C, benzoyl peroxide was diluted with solvent previously heated to 70°C.

Preparation of Suspensions for Stability Studies. Benzoyl peroxide suspensions were prepared at 10% (w/w) in 10-ml glass culture tubes with Teflon-lined closures. In each case, 200 mg of benzoyl peroxide was added to 1.8 g of solvent. The solvents used were PEG 400, PEG 400/water cosolvent mixtures (90, 80, 70, 60, and 30% PEG 400), PEG 400/propylene glycol (6:4), ethanol, propylene glycol, and water. All cosolvent mixtures were prepared by percentage (w/w). Suspensions were placed at ambient temperature and shaken on a weekly basis. At a specific time interval, acetonitrile was added to the culture tube, and the contents were dissolved, quantitatively transferred to a 250-ml volumetric, and diluted to volume. Samples were further diluted for HPLC measurement.

RESULTS AND DISCUSSION

Solubility. The solubility values of benzoyl peroxide obtained in this study appear in Table I. The solubility of benzoyl peroxide in mixtures of PEG 400 and water decreased as the ratio of water in the mixture increased. A 67,000-fold increase in solubility was observed from 10% PEG 400 (0.6 μg/g) to PEG 400 (40 mg/g). Gorman and Hall showed that linear relationships are obtained for plots of log mole fraction of solute versus dielectric constant of the solvent blend (10). Further, plots of log mole fraction of secobarbital in blends of ethanol/water, propylene glycol/water, and glycerol/water versus dielectric constant produced three separate regression lines (10). These authors concluded that although linear relationships of solubility and dielectric constant may exist for a compound in a specific solvent blend, this relationship may be quantitatively different for different solvent blends. However, this present study leads to a different conclusion. When the log mole fraction of benzoyl peroxide, calculated from the solubility values, was plotted versus the dielectric constant for the various solvents and solvent blends, a single linear relationship was observed ($r = 0.991$, $P = 0.001$) with the following calculated regression equation: log mole fraction = 0.191 − 0.103 * DEC (Fig. 1). Hence, it should be possible to estimate the solubility of benzoyl peroxide in various solvent blends of ethanol, propylene glycol, PEG 400, glycerol, and water using the calculated regression equation if the dielectric constant of the blend is known. Experimentally, the solubility of benzoyl peroxide in water was below the detection level of the assay method (0.5 μg/ml); however, an extrapolation from the solubility values of the PEG 400 blends suggests the approximate solubility of benzoyl peroxide in water to be 0.2 μg/g.

Solution Stability. Benzoyl peroxide in solution degraded in all the solvents studied, varying depending on the solvent type and concentration of benzoyl peroxide. In some instances, decomposition was not a simple first-order process. The calculated reaction half-lives are given in Table II.

Rapid degradation occurred in PEG 400 but was much slower in ethanol and propylene glycol. The degradation of benzoyl peroxide in PEG 400 (0.5 mg/g), ethanol, and propylene glycol exhibited first-order kinetics, with calculated half-lives of 1.4, 29, and 53 days at 40°C, respectively. Alcohols and ethers are able to accelerate the decomposition of benzoyl peroxide by the process called chain transfer (3,4,6). A solvent radical is formed when a benzoate radical ab-

Table I. Solubility of Benzoyl Peroxide in Various Solvents

Solvent	Solubility (mg/g) determination 1	2	Dielectric constant
PEG 400	39.6	40.0	14.4
PEG 400/water			
9:1	15.9	12.5	23.0
8:2	2.47	2.51	30.3
7:3	1.30	1.70	36.9
6:4	0.288	0.388	43.2
5:5	0.127	0.129	48.2
4:6	0.0377	0.0377	55.8
3:7	0.0124	0.0124	60.2
2:8	0.00325	0.00329	62.2
1:9	0.000528	0.000628	69.2
PEG 400/propylene glycol (6:4)	19.2	16.0	19.9
Ethanol	17.9	17.7	24.9
Ethanol/water (1:1)	0.77	0.76	46.5
Propylene glycol	2.95	2.95	28.3
Propylene glycol/water (75:25)	0.36	0.37	43.5
Glycerine	0.15	0.15	42.5[a]
Water	0.000155[b]		78.5[a]

[a] Value obtained from NBS circular 514.
[b] Extrapolated estimate.

stracts a proton from the solvent, forming benzoic acid as a degradation product (Scheme I). Benzoic acid was identified as a degradation product in this study (Fig. 2). The solvent radical is able to propagate a chain reaction by reacting with benzoyl peroxide. If the solvent radical formed is more stable than the benzoate radical and therefore less reactive, then the effect will be to suppress the chain decomposition. However, if the chain transfer to the solvent yields a new radical comparable in activity to the benzoate radical, then the effect will be to accelerate the decomposition of benzoyl peroxide. In the case of ethers, radicals are formed from the abstraction of a hydrogen bonded to the methylene carbon. For example, Cass (3) showed that the degradation products of benzoyl peroxide in 1,2-diethoxyethane were a mixture of carbon dioxide, benzoic acid, and two isomeric acylals, 1-(2-ethoxyethoxy) ethyl benzoate and 1,2-diethoxyethyl benzoate, with recovered yields of 0.18, 0.79, and 0.90 mol per mol of benzoyl peroxide decomposed, respectively. The recovery of the two acylals suggested that radical cleavage occurred at the C–H bond rather than the C–O bond. In the case of alcohols, it has been shown that the chain reaction involves attack by the benzoate radical upon the C–H bond of the alcohol in the alpha position of the oxygen, with the major degradation product being aldehyde and benzoic acid. This reactive pathway may be similar in PEG 400 but could be more complicated since PEG 400 contains between 8.2 and 9.1 ethyleneoxide units and 2 hydroxy units per molecule.

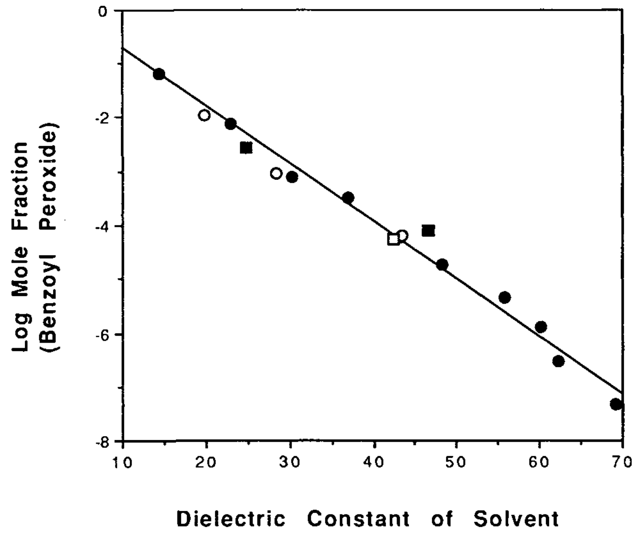

Fig. 1. The log mole fraction of benzoyl peroxide in hydroxy-containing solvents at room temperature: PEG 400 blends (●), propylene glycol blends (○), ethanol blends (■), and glycerol (□).

Reaction orders in PEG 400 and PEG 400/water blends were found to be dependent on the benzoyl peroxide concentration. The higher-concentration sample (1.5 mg/g) degraded at an accelerated rate compared to the low-concentration sample (0.5 mg/g). This effect is shown in Fig. 3. At a low concentration (0.5 mg/g), the kinetic data were best fitted to a first-order plot (Fig. 4), whereas at a higher concentration (1.5 mg/g), the data were best fitted to a three-halves-order plot. A three-halves-order reaction was indicated by obtaining a linear plot when the inverse of the square root of concentration of benzoyl peroxide was plotted against time. The slope change seen in Fig. 4 for the degradation of benzoyl peroxide in 70 and 80% PEG 400 at 25°C did not occur at other elevated temperatures and is explained later. In PEG 400 at 25°C, the calculated half-life increased by more than a factor of two when the concentration of benzoyl peroxide was decreased from 1.5 mg/g (6.3 days) to 0.5 mg/g (16 days). Better stability at lower benzoyl peroxide concentration was also observed in 90% PEG 400, with a

Table II. Reaction Rate Half-Lives (Days) for Benzoyl Peroxide in Solution

			Calculated reaction rate half-life (days) at			
Solvent system	Reaction order	Conc. (mg/g)	25°C (*r*)	40°C (*r*)	50°C (*r*)	70°C (*r*)
PEG 400						
100%	1.0	0.50	16.0 (0.999)[a]	1.40 (0.993)	0.70 (0.996)	0.07 (0.994)
90%	1.0	0.50	22.0 (0.999)	1.50 (0.992)	0.70 (0.996)	0.07 (0.993)
80%	1.0	0.50	29.0[b]	2.60 (0.997)	1.10 (0.999)	0.07 (0.989)
70%	1.0	0.50	47.0[b]	3.80 (0.995)	1.60 (0.991)	0.07 (0.993)
100%	1.5	1.50	6.3 (0.996)	0.71 (0.987)	0.25 (0.998)	—[c]
90%	1.5	1.50	11.0 (0.995)	0.65 (0.998)	0.24 (0.999)	—
PEG 400, propylene glycol (6:4)	1.5	1.80	19.2 (0.987)	0.57 (0.997)	0.26 (0.997)	—
Ethanol	1.0	2.60	266[d] (0.984)	29.00 (0.997)	17.00 (0.997)	—
Propylene glycol	1.0	2.00	247[d] (0.992)	53.00 (0.992)	25.40 (0.999)	—

[a] Reaction rate order correlation coefficient.
[b] Value obtained graphically.
[c] No value at this temperature.
[d] Less than 23% degradation after 90 days.

half-life of 22 days at 0.5 mg/g, compared to 11 days at 1.5 mg/g. This concentration effect on reaction rate was also observed by Gupta (11) in cosolvent mixtures of propylene glycol and acetone (1:1) at benzoyl peroxide concentrations of 1.0 and 0.1% (w/v).

The change in reaction order can be explained by understanding the kinetics of a free radical reaction (6,8). The kinetics of the decomposition of benzoyl peroxide depends on application of the steady-state approximations with regard to the radical intermediates. Such intermediates, benzoate- and solvent-derived radicals, are highly reactive, and their concentrations are considered to be constant throughout the reaction. The result of the steady-state conditions is that the rate of initiation equals the rate of termination. If this were not the case, free radicals would be present at high concentrations. Assuming that termination occurs between two solvent radicals $[S^\bullet]$ as shown in Scheme I, the following equation is derived (8):

$$\text{Rate} = k_{2p2}(k_i/2k_{t3})^{1/2}\,[\text{BP}]^{3/2} \qquad (1)$$

which is three-halves order with respect to benzoyl peroxide concentration. In the case where termination occurs between a benzoate-derived radical and a solvent radical, the following rate equation is derived:

$$\text{Rate} = (k_i k_{2p1} k_{2p2}/k_{t2})^{1/2}\,[\text{S}]^{1/2}[\text{BP}] \qquad (2)$$

which is first order with respect to BP concentration. The derivation of Eq. (2) is given in the Appendix. The effect of solvent type on reaction order is evident by comparing the reaction order of benzoyl peroxide in propylene glycol and a cosolvent mixture of PEG 400 and propylene glycol (6/4). In propylene glycol the reaction followed first-order kinetics, compared to three-halves-order kinetics in PEG 400/propylene glycol. It is obvious that the reaction is terminated by the coupling of two solvent radicals by the addition of PEG 400 to propylene glycol.

It was also observed that as the temperature was increased from 25 to 70°C, the disparity between reaction half-life, at the different PEG 400 blends, became less, such that with benzoyl peroxide concentrations of 0.5 mg/g at 70°C and 1.5 mg/g at 50°C, there were no measurable differences in half-life. At elevated temperatures thermal decomposition is more facile. Hence the chain length of the overall reaction may become less, remembering that chain length is defined as the number of propagation steps per initiation step. Therefore, at elevated temperatures the differences in solvent composition for the PEG 400 blends become less important.

At 25°C the degradation of benzoyl peroxide solutions containing 70 and 80% PEG 400, when plotted as first-order reactions, exhibited a lag phase, after which the reaction rate increased after approximately 14 days for 80% PEG 400 and 21 days for 70% PEG 400. The lag phase may represent the initiation reaction (Scheme I), which is characteristic of most free radical reactions (12). Here, the initiation reactions represent the thermal decomposition of benzoyl peroxide. The degradation rate increases after enough solvent radicals and benzoyl peroxide-derived radicals, which are more reactive, are generated to facilitate radical propagation. In PEG 400 and 90% PEG 400 at 25°C, the initiation reaction may occur more rapidly relative to the 70 and 80% PEG 400 solutions and is not readily observable.

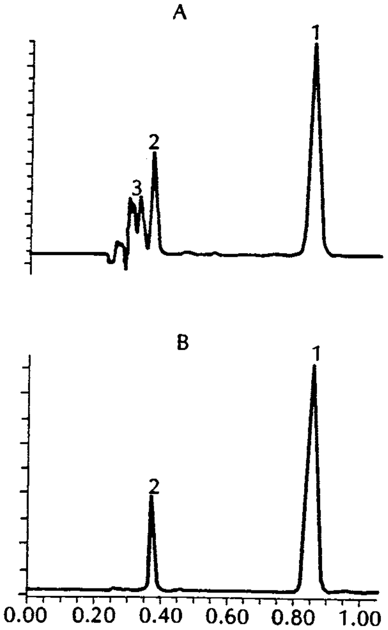

Fig. 2. Chromatograms of benzoyl peroxide and benzoic acid (A) when stored at 70°C for 4 hr in PEG 400 and (B) standard solution of benzoyl peroxide and benzoic acid (100 mg/ml). (1) Benzoyl peroxide; (2) benzoic acid; (3) unknown products.

Suspension Stability. The stability of benzoyl peroxide suspensions in various solvents appears in Table III. Benzoyl peroxide was most stable in water, propylene glycol, and PEG 400/water (30/70) and least stable in PEG 400. The addition of water to PEG 400 enhanced the stability such that, in a suspension containing 70% water, there was no observed degradation after 90 days. This result could be due in part to the concentration of benzoyl peroxide in solution as determined by solubility. Indeed, when the solubility of benzoyl peroxide was plotted against the corresponding reaction rate in PEG 400 and PEG 400 water blends, a correlation was found to exist (r = 0.989, P = 0.05) (Fig. 5). No degradation was observed in propylene glycol after 90 days, but when propylene glycol was added to PEG 400 the rate of degradation averaged 0.78% per day.

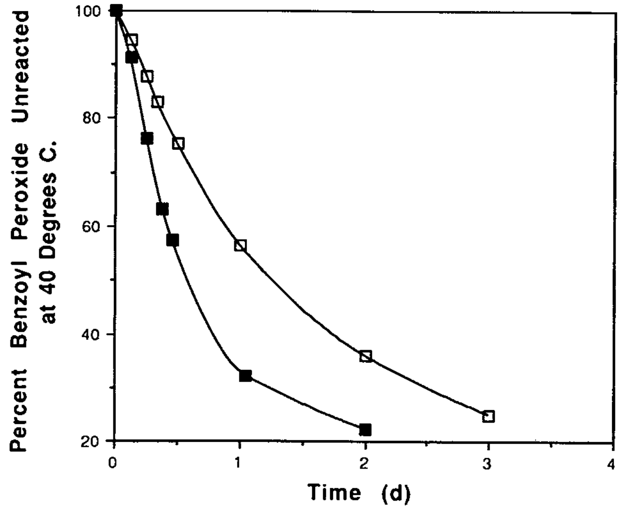

Fig. 3. The effect of concentration on the degradation of benzoyl peroxide in PEG 400: 0.5 mg/ml (□) and 1.5 mg/g (■).

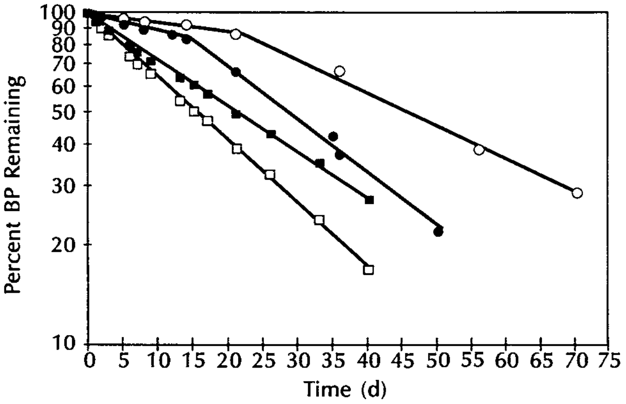

Fig. 4. The effect of solvent blend on first-order degradation of benzoyl peroxide (0.5 mg/g) at 25°C in PEG 400 (□), 90% PEG 400 (■), 80% PEG 400 (●), and 70% PEG 400 (○).

A first-order reaction rate constant for benzoyl peroxide in ethanol at 25°C was calculated from the stability data of the benzoyl peroxide suspension. The decomposition of benzoyl peroxide in a 10% suspension of ethanol at 25°C was observed to be 0.05% over a 24-hr period. A 10% (w/w) suspension is equivalent to 100 mg of drug substance in 0.9 g of ethanol. Hence, the apparent zero-order rate constant, k_0, can be expressed as 0.0500 mg of benzoyl peroxide decomposed per g of suspension per day. The average solubility of benzoyl peroxide in ethanol was 17.8 mg/g (Table I). The apparent zero-order rate constant is related to the first-order reaction rate constant, $k_{25^\circ\mathrm{C}}$, by the following equation:

$$k_0 = k_{25^\circ\mathrm{C}} \times (\text{BP solubility}) \tag{3}$$

$$k_0 = k_{25^\circ\mathrm{C}} \times (17.8\ \text{mg/g}) \tag{4}$$

$$k_{25^\circ\mathrm{C}} = 0.0028\ \text{day}^{-1} \tag{5}$$

This $k_{25^\circ\mathrm{C}}$ for suspension is in agreement with the experimental solution reaction rate constant of 0.0026 day^{-1} for benzoyl peroxide in ethanol (Table II).

Table III. Degradation of Benzoyl Peroxide (BP) in Suspensions (10%, w/w) at 25°C

Solvent	Decomposition rate determination (% BP/g/day) 1	2
PEG 400	3.5	3.5
PEG 400		
90%	1.4	1.8
80%	0.66	0.76
70%	0.29	0.29
60%	0.02	0.02
30%	—[a]	
Water	—	
PEG 400/PG (6:4)	0.68	0.88
Ethanol	0.05	0.05
Propylene glycol	—	

[a] No change after 90 days.

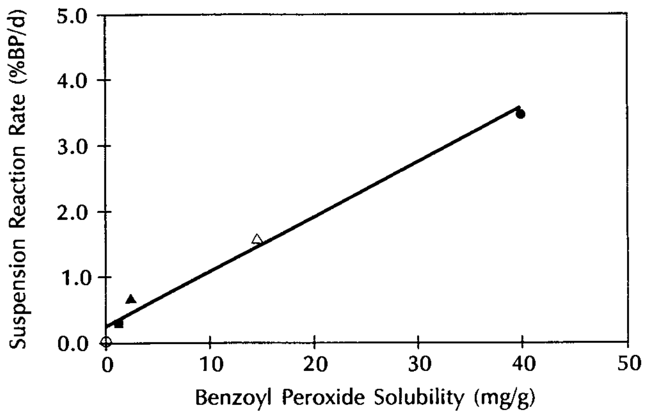

Fig. 5. The effect of benzoyl peroxide solubility of various PEG 400 and PEG 400 water blends on suspension reaction rates at room temperature: PEG 400 (●), 90% PEG 400 (△), 80% PEG 400 (▲), 70% PEG 400 (■), and 60% PEG 400 (○).

APPENDIX

The equation for the solvent-induced first-order decomposition of benzoyl peroxide [Eq. (2)] is derived by assuming that the overall reaction rate is that of either propagation step, with termination occurring by the coupling of a solvent radical with a benzoate-derived radical. Hence, in this example, using the propagation step where the solvent radical reacts with benzoyl peroxide, the rate of the overall reaction becomes

$$\text{Rate} = k_{2p2}[\text{BP}][\text{S}^\cdot] \tag{A1}$$

To solve for $[\text{S}^\cdot]$, the following steady-state approximations are made using k_{t2} for the termination step:

$$d[\text{P}^\cdot]/dt = 0 = 2k_i[\text{BP}] - k_{2p1}[\text{P}^\cdot][\text{S}] + k_{2p2}[\text{S}^\cdot][\text{BP}] - k_{t2}[\text{P}^\cdot][\text{S}^\cdot] \tag{A2}$$

$$d[\text{S}^\cdot]/dt = 0 = k_{2p1}[\text{P}^\cdot][\text{S}] - k_{2p2}[\text{S}^\cdot][\text{BP}] - k_{t2}[\text{P}^\cdot][\text{S}^\cdot] \tag{A3}$$

Therefore,

$$[\text{P}^\cdot] = (2k_i[\text{BP}] + k_{2p2}[\text{S}^\cdot][\text{BP}])/(k_{2p1}[\text{S}] + k_{t2}[\text{S}^\cdot]) \tag{A4}$$

$$[\text{S}^\cdot] = k_{2p1}[\text{P}^\cdot][\text{S}]/(k_{2p2}[\text{BP}] + k_{t2}[\text{P}^\cdot]) \tag{A5}$$

Substituting $[\text{P}^\cdot]$ in Eq. (A5) with Eq. (A4) yields the following quadratic equation:

$$k_{2p2}k_{t2}[\text{S}^\cdot]^2 + k_ik_{t2}[\text{S}^\cdot] - k_ik_{2p1}[\text{S}] = 0 \tag{A6}$$

which, when solved for $[\text{S}^\cdot]$, gives

$$[\text{S}^\cdot] = (k_ik_{2p1}k_{t2})^{1/2}\,[\text{S}]^{1/2}/k_{2p2}{}^{1/2}k_{t2} \tag{A7}$$

Substituting Eq. (A7) for $[\text{S}^\cdot]$ in Eq. (A1) yields the following rate equation:

$$\text{Rate} = (k_ik_{2p1}k_{2p2}/k_{t2})^{1/2}\,[\text{S}]^{1/2}\,[\text{BP}] \tag{A8}$$

which is first order with respect to benzoyl peroxide concentration.

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