Benzoyl Peroxide Stability in Pharmaceutical Gel Preparations

JAMES N. BOLLINGER [x], DELMA LEWIS, and VICTOR M. MENDEZ

Abstract □ The storage stability of benzoyl peroxide in the presence of both individual and combined pharmaceutical gel ingredients was investigated. Benzoyl peroxide was quite unstable in the presence of nucleophilic agents and certain acidic substances. At both 30 and 40° storage temperatures, benzoyl peroxide was destroyed rapidly (within 1 month) in the presence of ethanol and acidic chelating agents. The substitution of acetone for ethanol, the elimination of chelating agents, and the addition of sodium hydroxide to gel preparations markedly reduced degradation.

Keyphrases □ Benzoyl peroxide—stability in pharmaceutical gels, effect of temperature, pH, and various gel ingredients □ Stability—benzoyl peroxide in pharmaceutical gels, effect of temperature, pH, and various gel ingredients □ Gels—stability of benzoyl peroxide, effect of temperature, pH, and various gel ingredients □ Keratolytics—benzoyl peroxide, stability in pharmaceutical gels, effect of temperature, pH, and various gel ingredients

Benzoyl peroxide pharmaceutical preparations are widely used in the treatment of acne. However, due to the inherent chemical nature of benzoyl peroxide, degradation of these preparations is often encountered in storage. The purpose of this investigation, therefore, was to evaluate various parameters regarding the storage stability of benzoyl peroxide in pharmaceutical gel formulations.

BACKGROUND

A survey of existing products showed that most formulations contain either 5 or 10% benzoyl peroxide. The thickening agents commonly employed in the formation of the gels are carboxypolymethylene and hydroxypropyl methylcellulose. The stability of the gels formed with carboxypolymethylene is regulated by the addition of alkaline neutralizers such as sodium hydroxide, bis(2-propanol)amine, and triethanolamine. The stability of gels formulated with hydroxypropyl methylcellulose is usually enhanced by the addition of silicates.

Other gel components include the polyoxyethylene lauryl ether surfactants, which aid in the solubility of components in the gels themselves and enhance the contact of benzoyl peroxide with the skin. The latter effect probably is also enhanced by the presence of organic solvents.

Gels often contain various glycols such as glycerol, ethylene glycol, and propylene glycol. They serve several purposes including solvent action and humectant properties. The final major substance present is water, which may have a chelating agent added such as edetate disodium or citric acid.

Gels also may contain sodium lauryl sulfate, fragrances, and color, but these were not evaluated in this study.

Preliminary studies in this laboratory[1] indicated that certain ingredients in gels may influence the chemical stability of benzoyl peroxide—namely, that the benzoyl peroxide concentration is, with time, lowered due to its reactivity with the other ingredients. Original studies (1) on stability showed that, when heated, benzoyl peroxide, either in pure form or in nonpolar solvents, decomposed to yield carbon dioxide, biphenyl, phenyl benzoate, and benzene.

In the presence of alcohols, benzoyl peroxide decomposed to carbon dioxide, benzoic acid, and alcohol esters of benzoic acid (2). In the presence of acetic acid, it decomposed to form carbon dioxide, benzoic acid, phenylbenzoic acid, benzene, biphenyl, and phthalic acids (3). Since benzoyl peroxide is both a UV and a thermal free radical precursor, the resultant free radicals can interact with most molecules that, through electron shifts, are easily induced to possess reactive unshared electrons,

such as certain alcohols, sulfhydryl compounds, alkanes, alkenes, and aromatic compounds.

The purpose of this study was not to identify reaction products but to evaluate the decomposition of benzoyl peroxide with respect to whether any ingredient used in the gel preparations enhances its degradation.

EXPERIMENTAL

Formulations—As shown in Table I, experimental test formulations were made to evaluate the stability of benzoyl peroxides as influenced by thickening agents, alkaline neutralizers, surfactants, solvents, chelating agents, and temperature. Except for the alkaline neutralizers, all ingredients were added on a gram-weight basis. The ingredients were added together and thoroughly mixed to a uniform gel using a high speed, high shear mixer. The benzoyl peroxide suspension was prepared by adding water and micropulverizing the mixture into a milky, stable suspension.

The final concentration of the ingredients, including benzoyl peroxide, was adjusted prior to the final mixing through the addition of weighed amounts of water; neutralization and pH adjustments were made during the final mixing using approximately 5–10 ml of a 10% solution of the amines and 5–7 ml of a 10% NaOH solution. A zero-time analysis of benzoyl peroxide was performed in triplicate by titrimetric means (4) on each final test sample batch.

Experimental Protocol—The 22 gel formulations (Table I) were individually evaluated in triplicate at zero time and after storage for 30, 60, and 90 days at both 30 and 40°. Approximately 2.5 g of the test gel was placed in tared glass vials and sealed with polyethylene- or polycarbonate–polyethylene-lined screw caps. Each vial was then reweighed and stored in the dark in either the 30 or 40° oven. Therefore, 18 samples were prepared for each test of the 22 gel formulations; an additional vial containing 20 g of the gel was used to evaluate pH changes.

The concentration of benzoyl peroxide was determined as indicated by employing the recently developed titrimetric procedure (4, 5), using acetone extractions with potassium iodide–thiosulfate titrations in the presence of phenyl sulfide.

Sample weight losses due to storage were determined gravimetrically for each sample. Hydrogen-ion concentrations were determined using glass electrodes and a digital readout pH meter.

GLC[2] and GLC–mass spectrometry[3] were employed to identify any unusual reaction products.

RESULTS AND DISCUSSION

Figures 1–7 graphically depict the mean percentage loss of benzoyl peroxide as influenced by the various ingredients and combination of ingredients used in the gels.

The first six test samples were stored in glass vials with polyethylene caps; at the 40° test temperature, several samples stored with these caps lost substantial weight (10–20%) due to heat softening of the caps and subsequent solvent leakage. Subsequent analysis indicated, however, that this loss had no influence on the stability of benzoyl peroxide. Loss in sample weight usually ranged from 1 to 3% of the original weight.

Influence of Alkaline Neutralizers in Carboxypolymethylene Gel—These gel systems contained 1.75% carboxypolymethylene, 10% benzoyl peroxide, and enough triethanolamine, bis(2-propanol)amine, or sodium hydroxide solution to bring the pH to approximately 5. As shown in Fig. 1a, at 30° there was practically no breakdown of benzoyl peroxide over 90 days in any of these test samples. At 40° (Fig. 1b) and after 60 days, a 5–10% loss in benzoyl peroxide occurred. After 90 days at this temperature, the breakdown or loss was 20% in the presence of bis(2-propanol)amine, 10% with triethanolamine, and 5% with sodium hydroxide. The pH of the 40° samples over 90 days dropped approximately from 5 to 4.5.

[1] J. N. Bollinger, unpublished investigations, 1969 and 1974.

Table I—Experimental Test Formulations (All Included Water)

| Formulation	Thickening Agents	pH Regulator	pH	Organic Solvent	Surfactant	Humectant	Chelating Agent	Benzoyl Peroxide[a], %
1	Carboxypolymethylene[b] (1.75%)	Triethanolamine	5.02	—	—	—	—	10.88 ± 0.02
2	Carboxypolymethylene (1.75%)	Sodium hydroxide	4.85	—	—	—	—	11.02 ± 0.03
3	Carboxypolymethylene (1.75%)	Bis(2-propanol)amine	5.00	—	—	—	—	10.73 ± 0.05
4	Carboxypolymethylene (1.75%)	Triethanolamine	5.00	Ethanol (40%)	—	—	—	10.97 ± 0.26
5	Carboxypolymethylene (1.75%)	Sodium hydroxide	5.00	Ethanol (40%)	—	—	—	11.24 ± 0.05
6	Carboxypolymethylene (1.75%)	Triethanolamine	5.00	Acetone (10%)	—	—	—	11.25 ± 0.04
7	Carboxypolymethylene (1.75%)	Sodium hydroxide	4.85	Acetone (10%)	—	—	—	11.37 ± 0.02
8	Carboxypolymethylene (1.75%)	Triethanolamine	5.00	—	Polyoxyethylene 23 lauryl ether[c] (6%)	—	—	10.79 ± 0.03
9	Carboxypolymethylene (1.75%)	Triethanolamine	5.00	—	Polyoxyethylene 4 lauryl ether[d] (6%)	—	—	10.83 ± 0.14
10	Carboxypolymethylene (1.75%)	Triethanolamine	4.90	—	—	Propylene glycol (5%)	—	11.08 ± 0.04
11	Carboxypolymethylene (1.75%)	Triethanolamine	5.05	Ethanol (40%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.34 ± 0.06
12	Carboxypolymethylene (1.75%)	Triethanolamine	5.00	Ethanol (40%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Citric acid (0.1%)	11.46 ± 0.04
13	Carboxypolymethylene (1.75%)	Sodium hydroxide	4.90	Ethanol (40%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.43 ± 0.06
14	Carboxypolymethylene (1.75%)	Triethanolamine	4.95	Acetone (10%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.26 ± 0.05
15	Carboxypolymethylene (1.75%)	Triethanolamine	4.90	Acetone (10%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Citric acid (0.1%)	11.21 ± 0.07
16	Carboxypolymethylene (1.75%)	Sodium hydroxide	4.92	Acetone (10%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.40 ± 0.04
17	Hydroxypropyl methylcellulose (1%) and silicate[e] (1%)	Sodium hydroxide	6.15	—	—	—	—	11.56 ± 0.10
18	Hydroxypropyl methylcellulose (1%) and silicate (1%)	Sodium hydroxide	8.25	—	—	—	—	11.49 ± 0.05
19	Hydroxypropyl methylcellulose (1%) and silicate (1%)	Sodium hydroxide	5.95	Ethanol (40%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.39 ± 0.03
20	Hydroxypropyl methylcellulose (1%) and silicate (1%)	Sodium hydroxide	6.10	Acetone (10%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.53 ± 0.04
21	Hydroxypropyl methylcellulose (1%) and silicate (1%)	Sodium hydroxide	7.85	Ethanol (40%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.45 ± 0.07
22	Hydroxypropyl methylcellulose (1%) and silicate (1%)	Sodium hydroxide	7.95	Acetone (10%)	Polyoxyethylene 23 lauryl ether (6%)	Propylene glycol (5%)	Edetate disodium (0.1%)	11.39 ± 0.19

[a] Lucidol-70, Pennwalt. [b] Carbopol 940, B. F. Goodrich. [c] Brij 35, ICI America. [d] Brij 30, ICI America. [e] Colloidal magnesium silicate, Veegum, Vanderbilt.
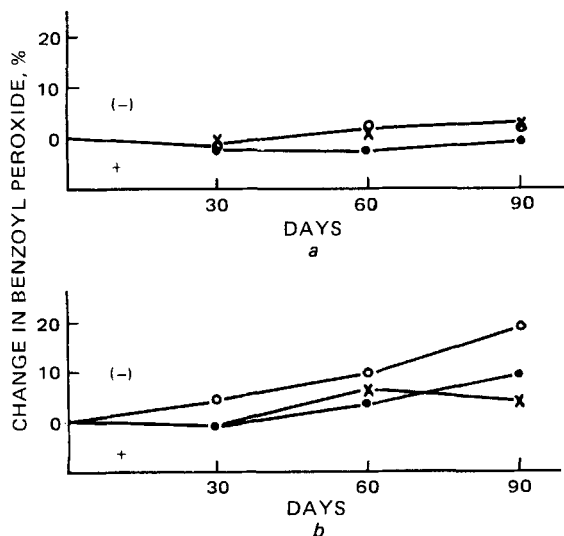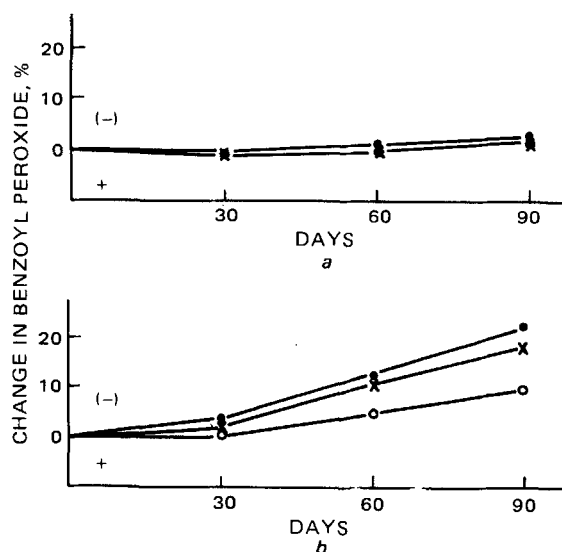
Figure 1—*Influence of alkaline neutralizers in carboxypolymethylene gel on the stability of benzoyl peroxide. Each gel consisted of carboxypolymethylene, benzoyl peroxide, and water. Alkaline neutralizers included triethanolamine (●), sodium hydroxide (X), and bis(2-propanol)amine (O). Key: a, storage at 30°; and b, storage at 40°.*

Influence of Organic Solvents—As shown in Fig. 2, two solvents, ethanol and acetone, were evaluated regarding their effect on benzoyl peroxide stability. The remainder of the preparation consisted of 10% benzoyl peroxide, 1.75% carboxypolymethylene, and both triethanolamine and sodium hydroxide as the polymer neutralizing-thickening agents.

At 30° (Fig. 2a), samples containing ethanol displayed 2–5% losses in benzoyl peroxide after 60 days. By 90 days, the samples containing ethanol and triethanolamine showed benzoyl peroxide losses of about 12%; those containing ethanol and sodium hydroxide had a 4% mean loss. None of the samples containing acetone showed measurable losses in benzoyl peroxide.
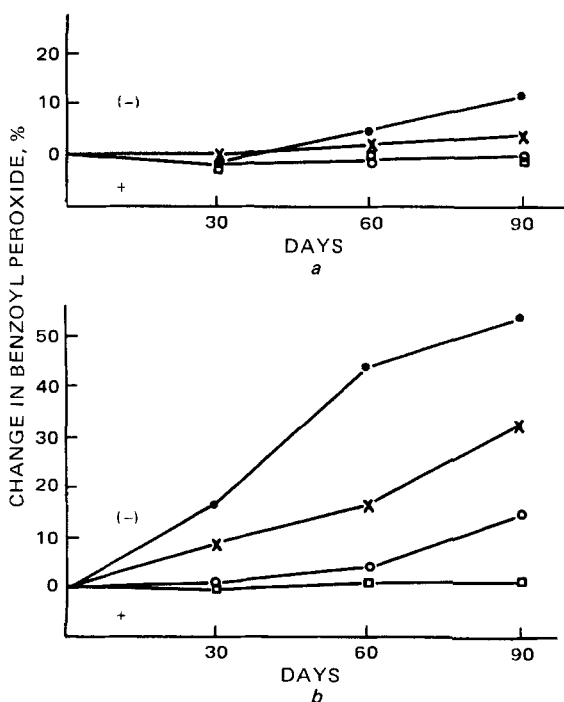
Figure 2—*Influence of organic solvents on benzoyl peroxide stability. Each gel mixture consisted of carboxypolymethylene, benzoyl peroxide, and water. Variants to the system included ethanol and triethanolamine (●), ethanol and sodium hydroxide (X), acetone and triethanolamine (O), and acetone and sodium hydroxide (□). Key: a, storage at 30°; and b, storage at 40°.*

Figure 3—*Influence of surfactant and humectant on the stability of benzoyl peroxide. Each gel mixture consisted of carboxypolymethylene, benzoyl peroxide, and water. Variants to the system included polyoxyethylene 23 lauryl ether (●), polyoxyethylene 4 lauryl ether (X), and propylene glycol (O). Key: a, storage at 30°; and b, storage at 40°.*

These same effects were accentuated at the 40° storage temperature. By 90 days, the ethanol–triethanolamine samples sustained a 50% loss in benzoyl peroxide, the ethanol–sodium hydroxide samples had a 33% loss, and the acetone–triethanolamine-containing samples had a 15% loss. Samples containing acetone–sodium hydroxide showed no loss in benzoyl peroxide (Fig. 2b).

Indicative of the breakdown of the benzoyl peroxide was a marked pH change (e.g., from a pH of 5 to ~3.5 in the ethanol–triethanolamine samples). After 90 days at 40°, samples containing ethanol–sodium hydroxide showed a decomposition of about 33% and the pH did not drop (from pH 5.0 to 4.2) as markedly.

Influence of Surfactant and Humectant—As shown in Fig. 3, neither the polyoxyethylene lauryl ethers nor propylene glycol appeared to influence the decomposition of benzoyl peroxide appreciably. After 90 days at 30°, there was no decomposition whatsoever; after 90 days at 40°, the decomposition of benzoyl peroxide was 20% in the presence of polyoxyethylene lauryl ethers as compared to 10% with propylene glycol.

Influence of Chelating Agents—These test systems contained all of the gel ingredients (Table I, Samples 11–16). The components held constant included carboxypolymethylene, polyoxyethylene lauryl ether, and propylene glycol. The ingredients that were varied included the solvents (ethanol and acetone), the neutralizers (sodium hydroxide and triethanolamine), and the chelating agents (edetate disodium and citric acid). It was not anticipated that any effect would be seen due to the chelating agents; however, as shown in Figs. 4 and 5, this assumption was erroneous.

Figure 4 graphically shows the influence of ethanol, triethanolamine, citric acid, and edetate disodium on the stability of benzoyl peroxide. The large decomposition of benzoyl peroxide (50–60%) at 30° after 90 days of storage (Fig. 4a) indicates that the chelating agents, citric acid and edetate disodium, somehow influenced the breakdown of benzoyl peroxide. The use of sodium hydroxide in this test system reduced the decomposition of benzoyl peroxide by more than 75% when compared to triethanolamine. The 15% level of decomposition noted in the sodium hydroxide-containing system was only slightly higher than that in the ethanol–sodium hydroxide system (5%) without chelating agents.

Figure 4b (40° test of the same mixtures) shows 90–100% destruction of benzoyl peroxide by 60 days, further indicating some form of catalytic activity due to the presence of chelating agents. The results were similar to the 30° test system discussed previously in that sodium hydroxide markedly delayed the decomposition of benzoyl peroxide during the initial 30 days.

Additional information on the effects of the solvent *versus* chelating agents can be seen in Fig. 5a. In these test systems, acetone was substituted for ethanol as the solvent. After 90 days at 30°, there was only a 10% decomposition in the acetone–triethanolamine–citric acid samples as
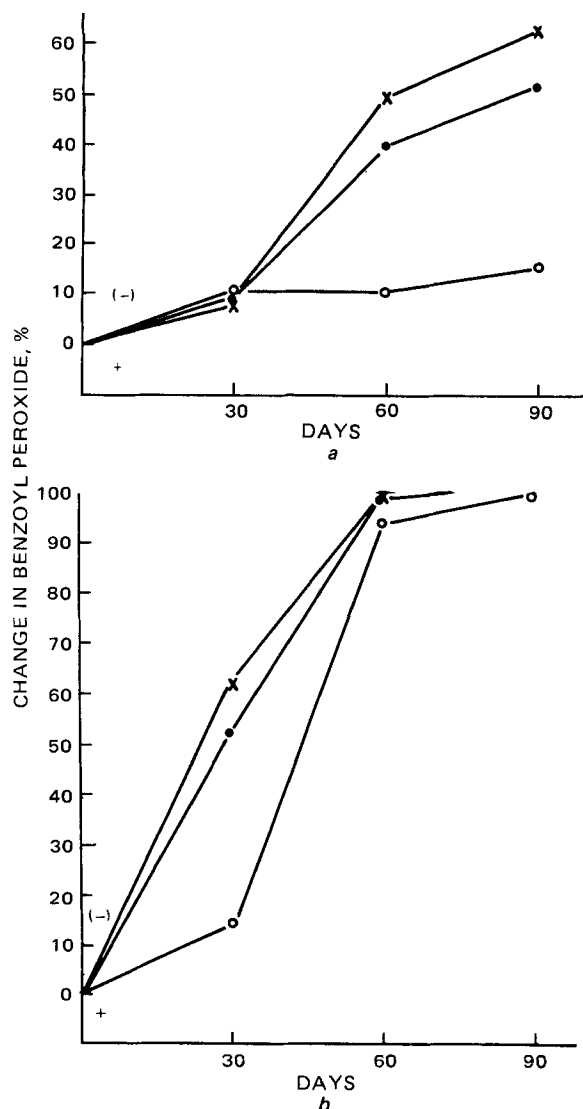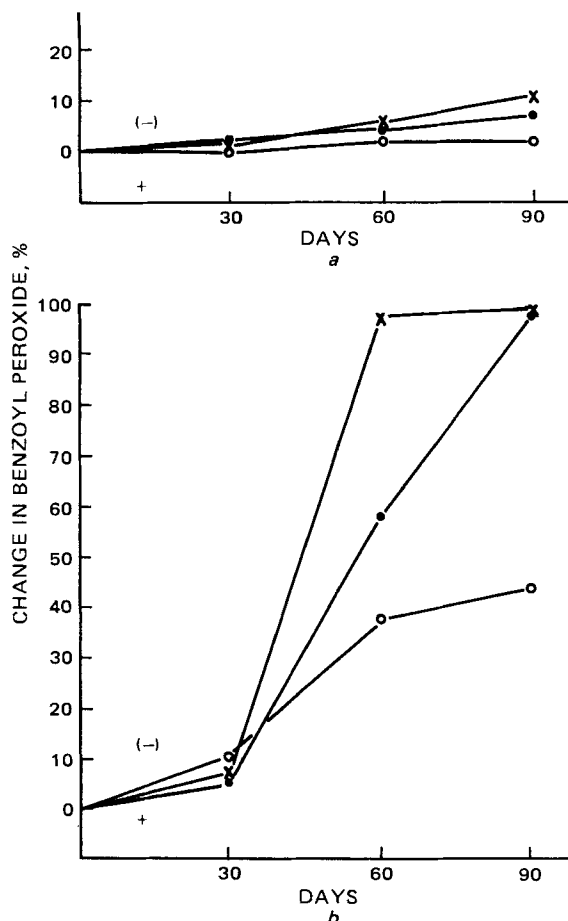
Figure 4—*Influence of ethanol in the presence of chelating agents on the stability of benzoyl peroxide. Each gel system contained carboxypolymethylene, benzoyl peroxide, ethanol, polyoxyethylene 23 lauryl ether, propylene glycol, and water. Variants in the system included triethanolamine and edetate disodium (●), triethanolamine and citric acid (X), and sodium hydroxide and edetate disodium (O). Key: a, storage at 30°; and b, storage at 40°.*

Figure 5—*Influence of acetone in the presence of chelating agents on the stability of benzoyl peroxide. Each test system consisted of the same ingredients as in Fig. 4, except that ethanol was replaced with acetone. Variants to the system included triethanolamine and edetate disodium (●), triethanolamine and citric acid (X), and sodium hydroxide and edetate disodium (O). Key: a, storage at 30°; and b, storage at 40°.*

compared to a 60% decomposition when ethanol was used in the same system. With the acetone–triethanolamine–edetate disodium system, there was a 7% decomposition of benzoyl peroxide but virtually no (<2%) decomposition in the acetone–sodium hydroxide–edetate disodium system.

Increasing the test storage temperature to 40° (Fig. 5b), however, induced the decomposition of benzoyl peroxide. During the initial 30 days of storage at this temperature, little decomposition occurred in any acetone sample; however, in the triethanolamine–citric acid–acetone system, there was 100% destruction of benzoyl peroxide by 60 days. It took 90 days to destroy benzoyl peroxide completely in the triethanolamine–edetate disodium–acetone system; with the sodium hydroxide–edetate disodium–acetone samples, only 45% destruction occurred after storage at 40° for 90 days.

These data indicate that the presence of chelating agents greatly enhanced the breakdown of benzoyl peroxide in the presence of ethanol. The partial decomposition noted in the presence of acetone and chelating agents at the higher temperatures was probably related to alcohol groups and other free-radical potentiating groups and not to acetone itself.

A GLC analysis of these samples indicated that the ethanol-containing preparations contained an additional reaction by-product. Both comparative GLC and GLC–mass spectrometry analysis showed this product to be ethyl benzoate.
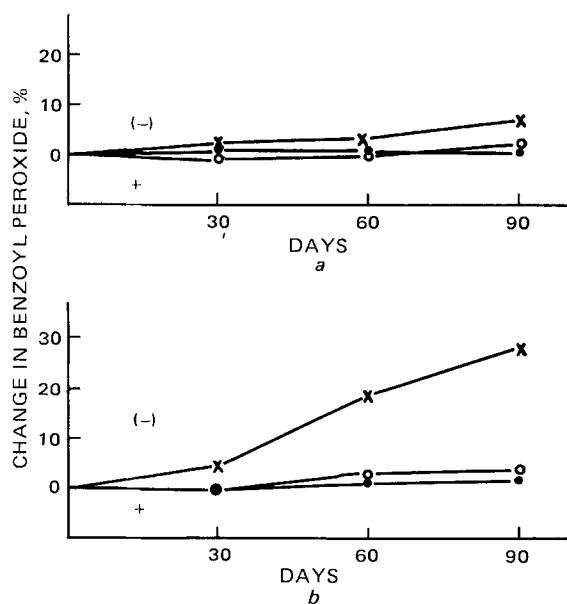
Influence of Hydroxypropyl Methylcellulose and Silicate—Samples 16–22 (Table I) contained hydroxypropyl methylcellulose and magnesium aluminum silicate as the thickening agents instead of carboxypolymethylene. As opposed to gel thickened with carboxypolymethylene (pH 5), these samples were stored at pH 6 and 8. The results of these tests are shown in Figs. 6 and 7. The exception to the use of complete formulations was that one group of samples, prepared and stored at pH 6 and 8, contained only benzoyl peroxide, hydroxypropyl methylcellulose, silicate, and sodium hydroxide.

The ethanol-containing samples were the only ones to show appreciable (30%) decomposition of benzoyl peroxide after storage for 90 days at 40° (Figs. 6 and 7). Whether the test samples were initially stored at pH 8 or 6 had no influence on the degree of breakdown. The pH of the samples stored at pH 6 dropped approximately 1.7 units and that of the samples stored at pH 8 dropped approximately 3.7 units, to yield an average pH for all samples of 4.3 regardless of whether the samples contained acetone, ethanol, or no solvents. The effects of the catalytic activity of the chelating agents was not as evident in this gel system. However, since sodium hydroxide was used to adjust the pH, the breakdown of benzoyl peroxide would not be expected to be as great as if triethanolamine had been employed.

Influence of Temperature versus Gel Ingredients—An evaluation of the data showed that the storage temperature had only an indirect influence on the stability of benzoyl peroxide. Even at storage temperatures of 40° (104°F), little degradation (1–3%) occurred if no free-radical propagating-type molecules were present in the mixture. Molecules that enhanced the free-radical propagation-type reactions included hydroxyl-containing molecules, primarily ethanol, and, indirectly, the chelating agents.

The fact that neutralization of the gel with sodium hydroxide markedly reduced degradation of benzoyl peroxide in the presence of ethanol and
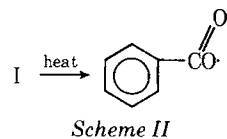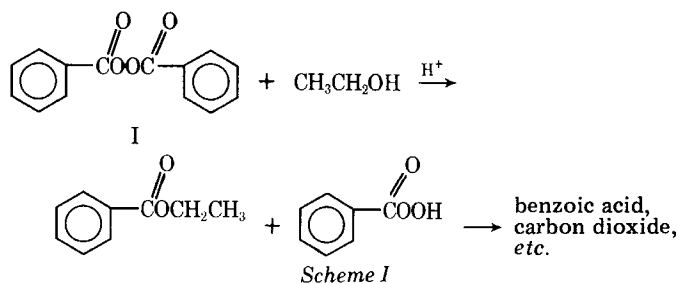
Figure 6—*Influence of hydroxypropyl methylcellulose and magnesium aluminum silicate gel system on the stability of benzoyl peroxide. The formulation contained benzoyl peroxide, sodium hydroxide, polyoxyethylene 23 lauryl ether, propylene glycol, edetate disodium, hydroxypropyl methylcellulose, magnesium aluminum silicates, and water. Variants to the system were: no solvent or chelating agent (●), ethanol as the solvent (×), and acetone as the solvent (○). Initial storage pH was 6.0. Key: a, storage at 30°; and b, storage at 40°.*

the chelating agents indicated that it interfered with the formation and entrance of ethanol radicals into the reaction. However, once the neutralization effect on the solvents is lost or lowered through either reaction with existing carboxyl groups or the thermal formation of benzoic acid (6), the entrance of free-radical propagating solvents such as ethanol into the reaction becomes increasingly unhindered. Acetone cannot readily, if at all, enter into free-radical reactions due to its electrochemical makeup. One might predict, based on data obtained in this study, that the polyoxyethylene lauryl ethers, glycols, carboxypolymethylene, and hydroxypropyl methylcellulose, in that order, can enter (on a limited basis) into a free-radical propagation-type reaction.
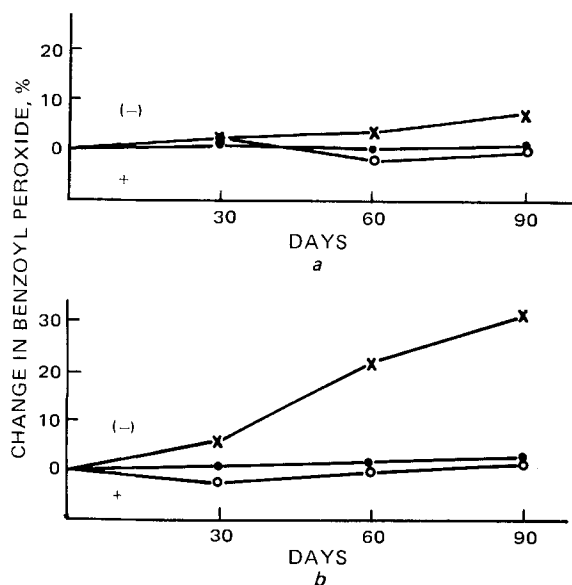
Figure 7—*Influence of pH on the storage stability of benzoyl peroxide in the hydroxypropyl methylcellulose-magnesium aluminum silicate gel. Basic gel system was the same as in Fig. 6, except that the samples were initially stored at a pH of 8. Variants were: no solvent or chelating agent (●), ethanol solvent (×), and acetone solvent (○). Key: a, storage at 30°; and b, storage at 40°.*

Scheme I

Scheme II

SUMMARY

The results of this investigation showed that triethanolamine, bis(2-propanol)amine, sodium hydroxide, carboxypolymethylene, hydroxypropyl methylcellulose, magnesium aluminum silicate, propylene glycol, the polyoxyethylene lauryl ethers, and acetone, individually, do not appreciably influence the storage stability of benzoyl peroxide (I). However, ethanol alone and, to a larger extent, in the presence of chelating agents and the carboxypolymethylene gel and, to a lesser degree, hydroxypropyl methylcellulose–silicate gel markedly enhanced the breakdown of benzoyl peroxide. The most pronounced degradation (100% within 30 days of storage at 30°) occurred in the presence of carboxypolymethylene, ethanol, and either edetate disodium or citric acid.

This latter phenomenon is thought to be due to the reaction shown in Scheme I. Classically, in the presence of heat, for example, benzoyl peroxide is thought to react as shown in Scheme II. However, the results of this investigation indicate that the Scheme II reaction did not occur to an appreciable extent even at the 40° storage temperature. Therefore, the partial degradation that occurred in the acetone samples containing the acidic chelating agents probably was due to some other alcohol or free-radical propagating groups, since acetone itself cannot be expected to react readily with benzoyl peroxide. In the absence of the chelating agents, for example, samples containing acetone were quite stable. In addition, the gel preparations containing sodium hydroxide as the neutralizing agent were far more stable than those containing triethanolamine, and the latter samples were slightly more stable than those containing bis(2-propanol)amine. These data indicate that sodium hydroxide hinders the formation of "solvent" radicals (i.e., $CH_3CH_2O\cdot + \cdot H$), thus slowing the propagation of benzoyl peroxide decomposition.

In general, the results of this investigation demonstrated that the stability of benzoyl peroxide in pharmaceutical gel preparations is strongly influenced by the chemical makeup of the formulations and, secondarily, by the storage temperature due to increased reactivity.

REFERENCES

(1) H. Erlenmeyer and W. Schoenauer, *Helv. Chim. Acta*, **19**, 338 (1936).

(2) H. Gelissen and P. H. Hermans, *Ber. Dtsch. Chem. Ges.*, **58**, 765 (1925).

(3) M. T. Gladstone, *J. Am. Chem. Soc.*, **76**, 1581 (1954).

(4) "First Supplement to the United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975.

(5) R. E. Daly, J. J. Lomner, and L. Chafetz, *J. Pharm. Sci.*, **64**, 1999 (1975).

(6) M. Gruber, R. Klein, and M. Foxx, *ibid.*, **58**, 566 (1969).

ACKNOWLEDGMENTS AND ADDRESSES