protein binding. Such inhibitors exist in normal subjects and accumulate in patients with impaired or absent renal function (15, 16). It is not unreasonable to assume that these inhibitors compete with and, therefore, reduce the protein binding of certain drugs in serum as well as in tissues such as the liver. If that is so, a correlation of serum and liver free fraction values for a drug is to be expected.

The results obtained with dicumarol are consistent with those for warfarin: pronounced intersubject differences in liver free fraction values, a positive correlation of these values with the serum free fraction values, and, consequently, relatively little variation of liver to serum concentration ratios. It would be inappropriate to ascribe the lower liver to serum concentration ratios of dicumarol, as compared to those of warfarin, to the more extensive serum protein binding of the former. Obviously, tissue to serum concentration ratios depend on the relative binding of the drug in both phases.

In the case of dicumarol, there exists a pronounced concentration dependence of liver to serum concentration ratios at serum concentrations below about 7 μg/ml (3). At the lowest concentration studied, that ratio was about 5. The decrease in the liver to serum concentration ratio of dicumarol with increasing concentration (in the low serum concentration range) may be due to saturation of certain binding sites in the liver; it could also be a consequence of a cooperative effect of dicumarol binding on serum albumin at concentrations below 10 μg/ml (17, 18). Above that concentration, the serum free fraction of dicumarol remains essentially constant over a wide concentration range (11). Tissue to serum concentration ratios above unity can also occur if there exists an active "uphill" transport process from blood to the liver or within the liver. If that were the case, it would be impossible to calculate liver free fraction values as done here. It is unlikely that there would be a correlation between serum free fraction values and liver free fraction values if the latter were only apparent values, reflecting the kinetic parameters of a specialized transport process (unless, of course, the endogenous inhibitors presumed to be responsible for interindividual differences in free fraction values compete with warfarin and dicumarol for binding sites on serum proteins as well as for sites in the transport process).

The experimental studies required to resolve these frustrating uncertainties are very formidable and technically complex. However, until the resolution of these open questions, so-called physiologically based pharmacokinetic models for protein-bound drugs provide only limited capability for describing and predicting the characteristics of drug distribution processes in the body.

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# Fenoprofen: Drug Form Selection and Preformulation Stability Studies


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Received September 17, 1976, from *Lilly Research Laboratories, Indianapolis, IN 46206.* Accepted for publication May 13, 1977.

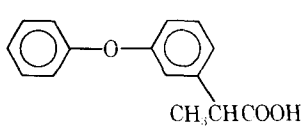


**Abstract** □ Several fenoprofen salts were prepared to obtain the most acceptable form for an oral dosage formulation. Thermal analysis techniques were used to compare stabilities of the water of hydration in different salt forms and to assess the effects of the water of hydration on compatibility with propoxyphene and codeine salts. Photodegradation products of fenoprofen were isolated and identified, and their relevance to product formulation was evaluated.



**Keyphrases** □ Fenoprofen—various salts synthesized, evaluated as oral dosage forms, stability studies □ Dosage forms, oral—various fenoprofen salts evaluated, stability studies □ Stability—various fenoprofen salts evaluated as oral dosage forms □ Anti-inflammatory agents—fenoprofen, various salts synthesized, evaluated as oral dosage forms, stability studies

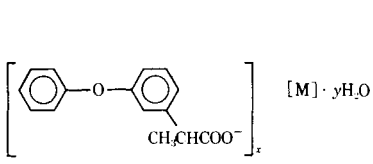

Fenoprofen, (±)-α-methyl-3-phenoxybenzeneacetic acid (I), is a nonsteroidal, anti-inflammatory, analgesic, and antipyretic agent[1]. The pharmacology of fenoprofen was described previously (1), and absorption, metabolism, and excretion patterns in humans were reported (2, 3). Fenoprofen is safe and effective in the symptomatic treatment of rheumatoid arthritis (4–6) and is also useful for its analgesic (7) and antipyretic (8) effects.

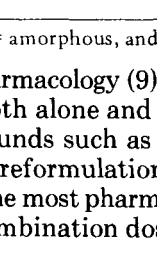
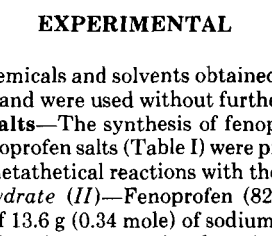
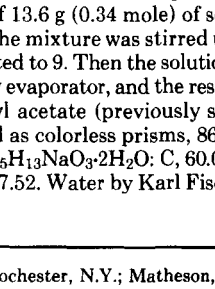



I

[1] Nalfon, fenoprofen calcium, developed by Lilly Research Laboratories.

Table I—Salts of Fenoprofen



| Compound | M | x | y | Physical[a] Form | Water Solubility, mg/ml | Humidity Stability |
|---|---|---|---|---|---|---|
| II | $Na^+$ | 1 | 2 | C | >200 | Fair |
| III | $Na^+$ | 1 | 0 | A | >200 | Very poor |
| IV | $K^+$ | 1 | ? | C | >200 | Very poor |
| V | $Ca^{2+}$ | 2 | 2 | C | 2.5 | Very good |
| VI | $Ca^{2+}$ | 2 | 1 | A | 2.5 | Poor |
| VII | $Ca^{2+}$ | 2 | 0 | A | 2.5 | Poor |
| VIII | $Mg^{2+}$ | 2 | 0 | — | >200 | — |
| IX | $Al(OH)^{2+}$ | 2 | 0 | A | 0.1 | Very good |
| X | $Al(OH)_2^+$ | 1 | 0 | A | 0.1 | Very good |
| XI | $NH_4^+$ | 1 | 0 | C | >200 | Very poor |
| XII | $HOCH_2CH_2N^+H(CH_3)_2$ | 1 | 0 | O | — | — |
| XIII | $HOCH_2CH_2N^+(CH_3)_3$ | 1 | 0 | C | >200 | Very poor |
| XIV | $C_6H_5CH_2N^+H_3$ | 1 | 0 | C | 5 | Very good |
| XV |  | 1 | 0 | C | 100 | Very good |
| XVI | $H_2NC_6H_5COOCH_2CH_2N^+H(C_2H_5)_2$ | 1 | 0 | C | 6 | — |
| XVII |  | 2 | 0 | C | 0.1 | Very good |
| XVIII |  | 1 | 0 | O | — | — |
| XIX |  | 1 | 0 | C | 10 | — |

[a] C = crystalline, A = amorphous, and O = oil. Crystallinity, or lack thereof, was determined by X-ray diffraction patterns.

Preclinical pharmacology (9) indicated the utility of oral dosage forms, both alone and in combination with other analgesic compounds such as propoxyphene or codeine. In this study, a preformulation stability program was designed to select the most pharmaceutically acceptable form for single and combination dosage.

## EXPERIMENTAL

**Reagents**—All chemicals and solvents obtained commercially[2] were reagent (ACS) grade and were used without further purification.

**Preparation of Salts**—The synthesis of fenoprofen was described by Marshall (10). Fenoprofen salts (Table I) were prepared directly from the free acid or *via* metathetical reactions with the sodium salt.

*Sodium Salt Dihydrate (II)*—Fenoprofen (82.0 g, 0.34 mole) was added to a solution of 13.6 g (0.34 mole) of sodium hydroxide in 350 ml of deionized water. The mixture was stirred until solution was attained, and the pH was adjusted to 9. Then the solution was evaporated at 10 mm of pressure on a rotary evaporator, and the residue was recrystallized from 200 ml of "wet" ethyl acetate (previously saturated with water). The product was obtained as colorless prisms, 86.6 g, mp 80°.

*Anal.*—Calc. for $C_{15}H_{13}NaO_3 \cdot 2H_2O$: C, 60.00; H, 5.75; Na, 7.66. Found: C, 59.82; H, 6.12; Na, 7.52. Water by Karl Fischer titration: calc., 12.00%; found, 11.9%.

[2] Eastman Kodak, Rochester, N.Y.; Matheson, Coleman and Bell, Norwood, Ohio.

*Anhydrous Sodium Salt (III)*—All efforts to prepare crystalline anhydrous fenoprofen sodium failed. Dehydration of the dihydrate under vacuum at 50° gave an amorphous form, which rehydrated at 20% relative humidity (RH) or above.

*Anal.*—Calc. for $C_{15}H_{13}NaO_3$: C, 68.17; H, 4.95. Found: C, 67.94; H, 5.25.

*Potassium Salt (IV)*—The procedure used for the sodium salt was followed using potassium hydroxide. Crystallization from ethyl acetate gave colorless needles of the potassium salt, which were, however, very hygroscopic under ambient conditions.

*Anal.*—Calc. for $C_{15}H_{13}KO_3$: C, 64.25; H, 4.67. Found: C, 63.82; H, 5.08.

*Calcium Salt Dihydrate (V)*—A solution of 60.0 g (0.2 mole) of fenoprofen sodium dihydrate in 300 ml of deionized water was treated dropwise with a solution of 11.1 g (0.1 mole) of calcium chloride in 100 ml of water. After stirring for 2 hr, the precipitated fenoprofen calcium was filtered off and air dried, 56.0 g, mp 105–110°. Recrystallization from 50% ethanol–water gave colorless needles, 45 g, mp 105–110°.

*Anal.*—Calc. for $C_{30}H_{26}CaO_6 \cdot 2H_2O$: C, 64.49; H, 5.41. Found: C, 64.41; H, 5.47. Water by Karl Fischer titration: calc., 6.45%; found, 6.43%.

*Anhydrous Calcium Salt (VII)*—All efforts to obtain a crystalline anhydrous calcium salt failed. Dehydration of the dihydrate under vacuum at 75° gave an amorphous anhydrous material, which rehydrated to the dihydrate at 60% RH or above.

*Anal.*—Calc. for $C_{30}H_{26}CaO_6$: C, 68.94; H, 5.01. Found: C, 69.10; H, 5.22.

Trituration of the dihydrate with absolute methanol gave what seemed to be fenoprofen calcium monohydrate (VI) (3.2% water by Karl Fischer titration), but the compound was amorphous and rehydrated at ambient conditions to crystalline dihydrate.

**Table II—Stability of Fenoprofen Salts to Relative Humidity**

| Relative Humidity, %[a] | Percent Weight Change | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | II[b] | III | V[c] | VI | VII | IX | XIV | XVII |
| 1 | −11.4 | −0.5 | 0.0 | — | 0.5 | 0.0 | 0.0 | −0.3 |
| 20 | +0.3 | +10.7 | 0.0 | +0.3 | +1.7 | — | 0.0 | −0.3 |
| 40 | +0.4 | +12.5 | 0.0 | +0.2 | +2.9 | 0.0 | 0.0 | −0.2 |
| 60 | — | — | — | +0.7 | +3.7 | — | — | — |
| 70 | +2.5 | +15.8 | 0.0 | — | — | — | 0.0 | −0.1 |
| 80 | — | — | — | +3.3 | — | — | — | — |
| 93 | +9.3 | +36.5 | 0.0 | — | +6.3 | 0.0 | 0.0 | 0.0 |

[a] Controlled humidity chambers were attained by means of saturated solutions of appropriate inorganic salts in closed containers. [b] Theory for dihydrate is 12.0% water. [c] Theory for dihydrate is 6.4% water.

*Magnesium Salt (VIII)*—The procedure used for fenoprofen calcium was followed with magnesium sulfate instead of calcium chloride. No precipitation occurred, and all efforts to crystallize the magnesium salt failed.

*Hydroxyaluminum Salt (IX)*—A solution of 16.0 g (0.053 mole) of fenoprofen sodium dihydrate and 2.01 g (0.024 mole) of sodium bicarbonate in 200 ml of deionized water was stirred and treated with a solution of 9.40 g (0.025 mole) of aluminum nitrate nonahydrate in 100 ml of water. Stirring was continued for 1 hr. Then the precipitated product was filtered off, washed with water, and dried at 75° (3 mm of pressure) for 12 hr.

*Anal.*—Calc. for $C_{30}H_{27}AlO_7$: C, 68.40; H, 5.20. Found: C, 67.90; H, 5.62.

*Dihydroxyaluminum Salt (X)*—A solution of 8.0 g (0.027 mole) of fenoprofen sodium dihydrate and 4.2 g (0.050 mole) of sodium bicarbonate in 150 ml of deionized water was stirred and treated with a solution of 9.40 g (0.025 mole) of aluminum nitrate nonahydrate in 100 ml of water. The precipitated product was filtered off and dried at 70° (3 mm of pressure) for 12 hr.

*Anal.*—Calc. for $C_{15}H_{15}AlO_5$: C, 59.60; H, 5.00. Found: C, 59.44; H, 5.07.

**Preparation of Amine Salts of Fenoprofen**—The preparations of numerous amine salts were attempted. Many gave oils or extremely hygroscopic solids. In general, an equivalent amount of the amine was added to fenoprofen acid dissolved in anhydrous ether. Crystallization of the salt was induced (when necessary) by addition of petroleum ether.

*Ammonium Salt (XI)*—Needles from ethyl acetate–petroleum ether were extremely hygroscopic.

N,N-*Dimethyl*-N-*(2-hydroxyethyl)ammonium Salt (XII)*—Compound XII was an oil.

*Choline Salt (XIII)*—Extremely hygroscopic crystals were obtained.

*Benzylammonium Salt (XIV)*—Colorless needles from ethyl acetate–petroleum ether were obtained, mp 107–108°.

*Anal.*—Calc. for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.33; H, 6.88; N, 3.93.

*Morpholine Salt (XV)*—Compound XV was obtained as colorless crystals from ethyl acetate–petroleum ether, mp 96–98°.

*Anal.*—Calc. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.14; H, 6.82; N, 4.25.

*Procaine Salt (XVI)*—Colorless prisms from ethyl acetate–hexane were prepared, mp 85°.

*Anal.*—Calc. for $C_{28}H_{34}N_2O_5$: C, 70.27; H, 7.16; N, 5.85. Found: C, 70.07; H, 7.06; N, 6.14.

N,N′-*Dibenzylethylenediamine Salt (XVII)*—Colorless crystals from ethanol were prepared, mp 103°.

*Anal.*—Calc. for $C_{46}H_{48}N_2O_6$: C, 76.22; H, 6.67; N, 3.87. Found: C, 76.28; H, 6.66; N, 3.91.

d-*Propoxyphene Salt (XVIII)*—This compound was a viscous oil.

*Codeine Salt (XIX)*—Compound XIX was obtained as light-tan crystals from ethyl acetate, mp 103–105°.

*Anal.*—Calc. for $C_{33}H_{35}NO_6$: C, 73.13; H, 6.51; N, 2.59. Found: C, 73.01; H, 6.61; N, 2.58.

**Solubility Measurements**—The UV absorption spectrum of fenoprofen sodium exhibited an absorption maximum at 270 nm. A standard absorbance–concentration curve was determined and used to estimate equilibrium solubilities of the inorganic salts of fenoprofen. The solubilities of amine salts were obtained by comparison with UV absorption curves of standard solutions of the respective salts. Saturated solutions were prepared by vigorous agitation of a mixture of a 2-g sample in 10 ml of deionized water at 25° for 24 hr followed by filtration. No attempt was made to determine solubilities above 200 mg/ml.

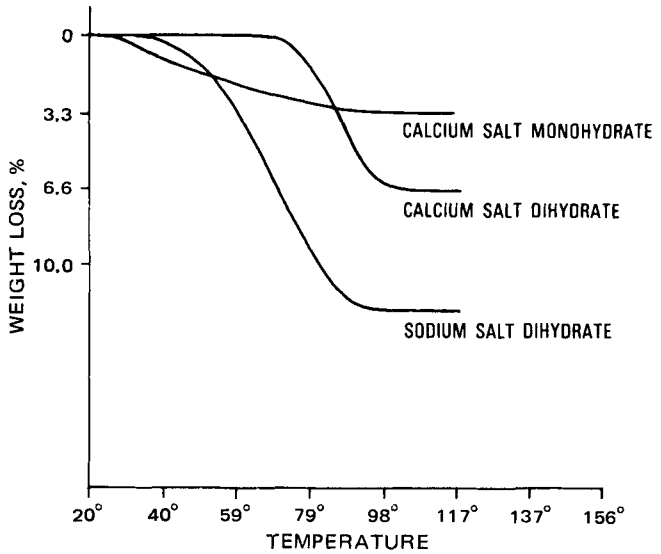



**Figure 1**—*Hydrate stability of fenoprofen salts by thermal gravimetric analysis.*

**Humidity Stability Measurements**—Preweighed samples were equilibrated in controlled humidity chambers for 48 hr at 25° and then reweighed to determine the gain or loss of weight. Samples were stored at several relative humidities ranging from 1 to 93% (Table II).

**Thermal Gravimetric Analyses (TGA)**—*Hydrate Stability*—Thermograms were obtained on a thermogravimetric analyzer under a controlled atmosphere (nitrogen sweep, 40 cm³/min) and a constant heating rate (5°/min)[3]. The temperature at which the weight loss began was taken as a relative measure of hydrate stability (Fig. 1).

*Compatibility with Analgesic Amine Salts*—Fenoprofen calcium dihydrate was triturated in a mortar with an equal amount of propoxyphene hydrochloride[4], propoxyphene napsylate (2-naphthalenesulfonate)[5], and codeine sulfate in separate experiments. Thermograms were obtained initially and after storage for comparison (Fig. 2).

**Differential Thermal Analysis (DTA)**—Thermal analysis curves were obtained using a differential scanning calorimeter[6]. Samples for analysis were prepared by trituration of the fenoprofen salt with the appropriate amine salt in a mortar. In one instance, a mixture of fenoprofen calcium dihydrate and propoxyphene hydrochloride was treated with a few drops of water, triturated, and allowed to dry under ambient conditions (Fig. 3). Analyses were carried out under a nitrogen atmosphere with a heating rate of 20°/min and a sensitivity of 5 mcal/sec. Samples were stored at 25° (45–60% RH), 37°(20–30% RH), and 50° (10–20% RH) and analyzed periodically for comparison (Figs. 3–5).

Simultaneous differential thermal and thermal gravimetric analyses[7] were carried out under nitrogen (40 cm³/min) and at a heating rate of 5°/min (Figs. 6 and 7).

**Photodegradation**—*Low-Pressure Mercury Lamp*[8]—An aqueous solution of fenoprofen sodium (25 mg/ml) was purged with nitrogen and exposed to the mercury lamp in a quartz immersion well with a filter[9]. In this apparatus, the exposed solution surrounds the lamp at an average distance of 5 cm. Samples were taken periodically, and fenoprofen was quantitated by GLC using a 0.61-m (2-ft) column of 3% methylphenyl silicone on Chromosorb G at 195°. The percentage decomposition ($t_{\%}$) with exposure time was: $t_{10}$, 2 hr; $t_{25}$, 8 hr; and $t_{40}$, 40 hr.

Exposed samples were subjected to TLC; spots were developed with benzene–acetic acid (10:1) on silica gel F-254 plates and visualized by short wavelength UV light or iodine vapors. Major components were observed with $R_f$ values of 0.15, 0.21, 0.25, 0.32, and 0.44 (fenoprofen). Minor components had $R_f$ values of 0.54 and 0.62. The minor components were neutral and were removed by extraction, separated by preparative TLC, and identified as *m*-phenoxyacetophenone ($R_f$ 0.54) and *m*-phenoxystyrene ($R_f$ 0.62) by comparison of spectral (IR and mass) characteristics with authentic samples. Two major components were isolated

[3] DuPont model 950.
[4] Darvon, Lilly.
[5] Darvon-N, Lilly.
[6] Perkin-Elmer DSC-2.
[7] Rigaku DT-TGA.
[8] Hanovia lamp (200-w).
[9] Vycor.

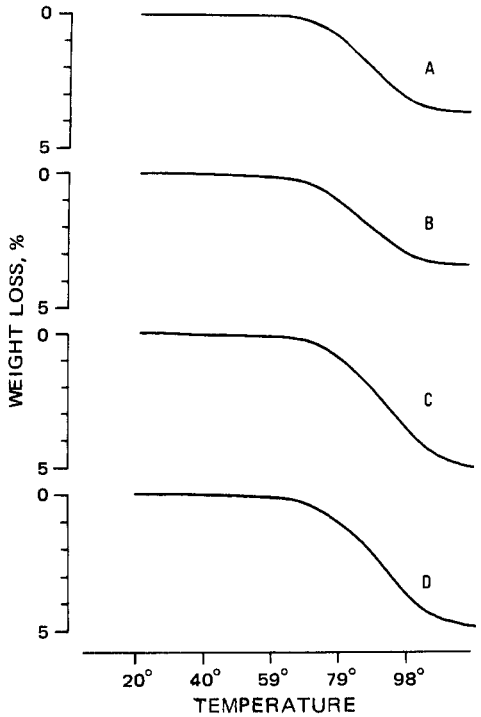



**Figure 2**—*Thermal gravimetric analysis curves of mixtures of fenoprofen calcium dihydrate with propoxyphene salts. Key: A, 1:1 mixture of fenoprofen calcium dihydrate and propoxyphene hydrochloride; B, sample of A stored 5 years at 25°; C, 1:1 mixture of fenoprofen calcium dihydrate and propoxyphene napsylate monohydrate; and D, sample of C stored 5 years at 25°.*

by column chromatography [silica gel, elution with benzene–acetic acid (10:1)] and analyzed by IR, NMR, and mass spectra. Identification of both components as isomeric hydroxybiphenylpropionic acids is detailed in the *Discussion* section.

Similar degradation occurred when a solution of fenoprofen (25 mg/ml) in isopropyl alcohol was exposed to the mercury lamp.

*Carbon-Arc Lamp*[10]—Aqueous solutions of fenoprofen sodium (25 mg/ml) were exposed in both Pyrex and quartz containers, and the absence of degradation was revealed by GLC. The percentage decomposition ($t_{\%}$) with time was $t_{0.5} > 96$ hr in either container. Although no quantitative degradation was seen by GLC, trace amounts of *m*-phenoxyacetophenone ($R_f$ 0.54) were detected by TLC. Spectral characteristics (IR and mass spectra) were the same as those of an authentic sample.

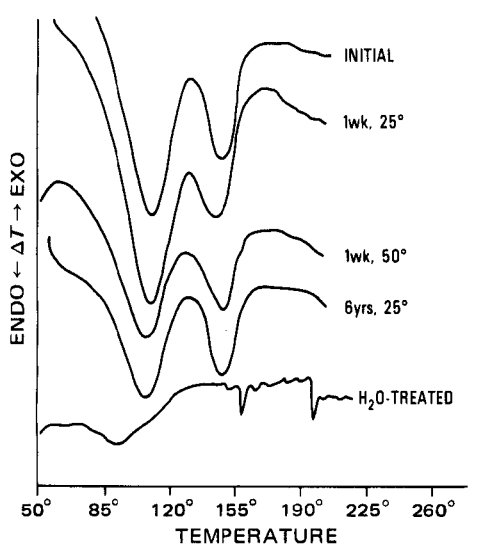



**Figure 3**—*Differential thermal analysis curves of fenoprofen calcium dihydrate–propoxyphene hydrochloride mixture showing effects of storage and of added water.*

[10] Fadeometer (5000 $\mu w/cm^2$).

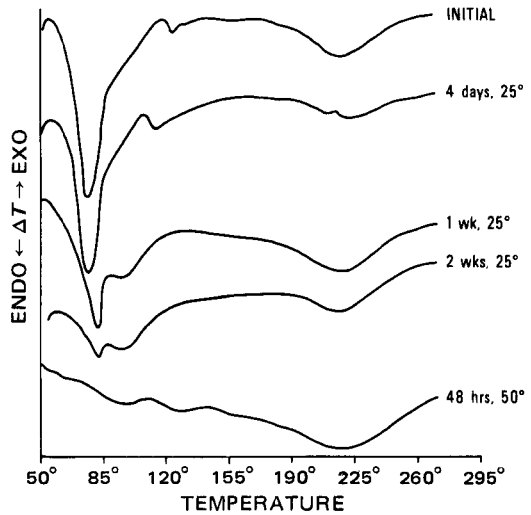



**Figure 4**—*Differential thermal analysis curves of fenoprofen sodium dihydrate–propoxyphene napsylate monohydrate mixture showing effect of storage.*

*Direct Sunlight*—A solution of fenoprofen (25 mg/ml) in isopropyl alcohol in a quartz container was exposed to direct sunlight for 1 week. IR analysis and TLC revealed no degradation.

## DISCUSSION

Fenoprofen free acid is unacceptable as an oral dosage form because of its low melting point (40°). A relatively high melting compound would avoid frictional heat problems associated with mechanical handling and eutectic melts in combination dosage forms. Therefore, salt forms of fenoprofen were prepared (Table I) and evaluated in terms of their physical characteristics, compatibility with propoxyphene and codeine salts, and chemical stability. Light stability and oxidation were specifically noted.

In many instances, fenoprofen salts could not be induced to crystallize. The sodium salt (II) was obtained as a crystalline dihydrate, but the anhydrous form (III) was amorphous. The potassium salt (IV) was crystalline but very hygroscopic. The calcium salt was crystalline as the dihydrate (V), whereas both the monohydrate (VI) and the anhydrous form (VII) were amorphous. Efforts to crystallize sodium and calcium derivatives from anhydrous solvents failed; crystallization occurred only when sufficient water was present to form dihydrates. The magnesium compound (VIII) could not be crystallized, and both aluminum deriva-

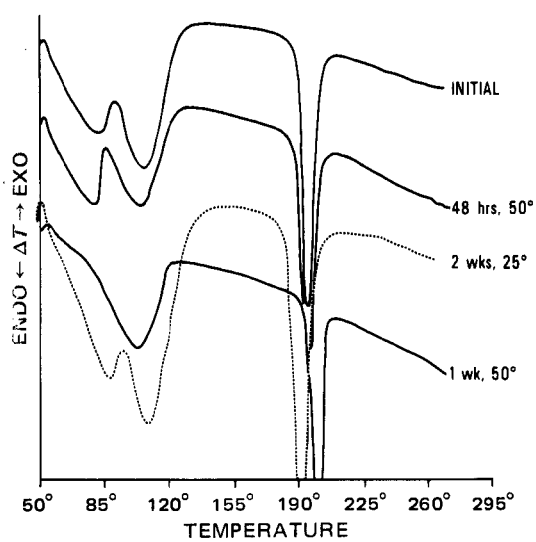



**Figure 5**—*Differential thermal analysis curves of fenoprofen calcium dihydrate–codeine sulfate pentahydrate mixture showing effect of storage.*

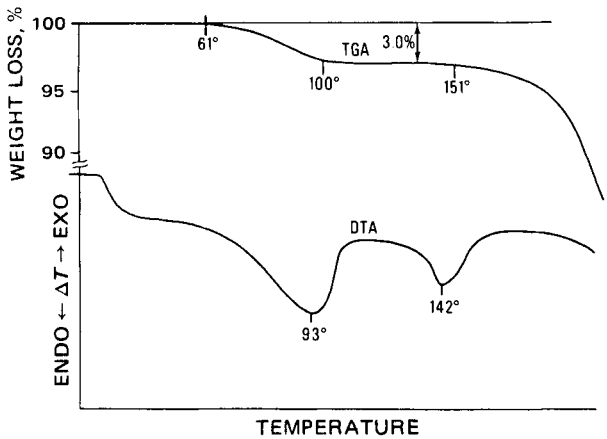



**Figure 6**—*Simultaneous differential thermal and gravimetric analyses of fenoprofen calcium dihydrate–propoxyphene hydrochloride mixture.*

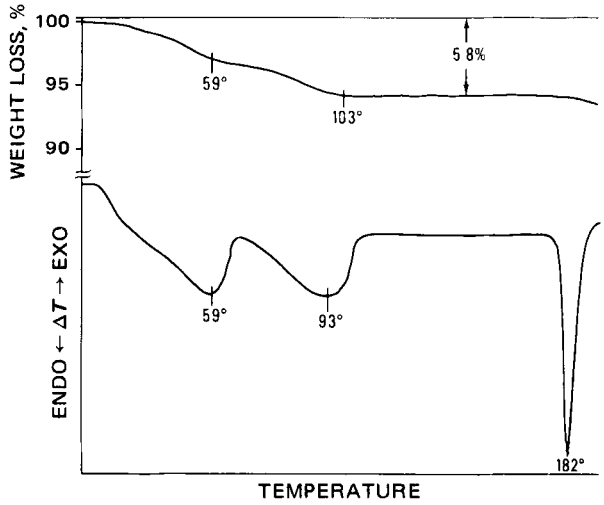



**Figure 7**—*Simultaneous differential thermal and gravimetric analyses of fenoprofen calcium dihydrate–codeine sulfate pentahydrate mixture.*

tives (IX and X) were amorphous and insoluble in water. Although initially considered too insoluble for capsule or tablet formulation, the aluminum salts were later found useful for oral suspension formulation (11).

A number of amine salts were prepared (Table I), but no advantages over sodium and calcium compounds were found. Organic amine salts were, therefore, excluded from further consideration because of the extensive toxicology studies and production costs involved. Preliminary data indicated the sodium salt dihydrate (II) and calcium salt dihydrate (V) to have the most suitable physical characteristics, *i.e.*, crystallinity and appreciable water solubility.

In evaluating drug form candidates for solid dosage formulations, the possible effects of changes in relative humidity upon physical stability must be considered. Table II demonstrates the sensitivities of several fenoprofen salts to changes in relative humidity. The sodium salt dihydrate lost both moles of water at 25° and 1% RH, but the calcium salt dihydrate was stable under these conditions. The anhydrous, amorphous sodium salt absorbed excessive amounts of water at high relative humidity, whereas both amorphous forms of fenoprofen calcium absorbed only enough water to form the crystalline dihydrate. Compounds IX, XIV, and XVII were stable over the humidity range studied but were not considered further for reasons already discussed.

Thermal gravimetric analysis was used to compare relative stabilities of the water of hydration. Samples were heated at a controlled rate in a defined atmosphere, and the percent weight losses were recorded as a function of temperature. The temperature at which weight loss began was taken as a measure of hydrate stability. Thermograms in Fig. 1 show that crystalline sodium salt dihydrate lost water at or near room temperature, but crystalline calcium salt dihydrate was stable to 70°. Amorphous calcium salt monohydrate, however, lost water at room temperature. These results indicated that the water of hydration was more tightly bound in calcium salt crystals than in sodium salt crystals. The integrity of the crystal structure of calcium salt dihydrate allows greater flexibility in formulation considerations.

Preclinical pharmacology indicated the potential utility of an oral dosage form combining fenoprofen with analgesic amines such as propoxyphene or codeine. Furthermore, it was desirable to mix the drugs in the formulation. Attempts to formulate fenoprofen sodium dihydrate with either propoxyphene salts (hydrochloride or napsylate) or codeine salts (sulfate or phosphate) failed. These combinations were chemically and physically incompatible. Intimate mixing caused eutectic melts and/or acid–base reactions in all instances.

In contrast, mixtures of fenoprofen calcium dihydrate with propoxyphene salts remained free-flowing powders indefinitely. Mixtures with codeine salts were also compatible. Although its relatively low water solubility contributed to this compatibility, the stability of the bound water of hydration of the calcium salt compared to that of the sodium salt was more significant. The integrity of crystalline structure of fenoprofen calcium dihydrate in the presence of propoxyphene or codeine salts is shown by both thermal gravimetric analysis and differential thermal analysis. Thermograms in Fig. 2 show that the crystallinity was unchanged after storage of mixtures of fenoprofen calcium dihydrate with either propoxyphene hydrochloride or propoxyphene napsylate. Similarly, mixtures of fenoprofen calcium dihydrate and codeine sulfate pentahydrate showed no change in crystallinity when stored for 8 months at 25°.

Differential thermal analysis is a useful technique for studying drug–drug interactions or drug–excipient interactions (12–14). In this study, differential thermal analysis proved useful in demonstrating the absence of an interaction between fenoprofen calcium dihydrate and propoxyphene salts. In Fig. 3, the endotherm peaking at 109° is due to the loss of crystallinity and volatilization of the water of hydration; the endotherm at 147° suggests a eutectic melt. Any acid–base reaction that could occur is not evident in the thermogram. Interaction did occur in aqueous systems to form a viscous oil at room temperature. The effect on the thermogram of adding excess water to the sample to force interaction is seen in the bottom curve of Fig. 3.

Data shown in Fig. 6 were obtained using an instrument[7] that simultaneously performs thermal gravimetric and differential thermal analyses. The top curve (thermal gravimetric analysis) shows a weight loss corresponding to the first endotherm in the lower curve (differential thermal analysis). The second endotherm is not associated with a weight loss and is consistent with a eutectic melt.

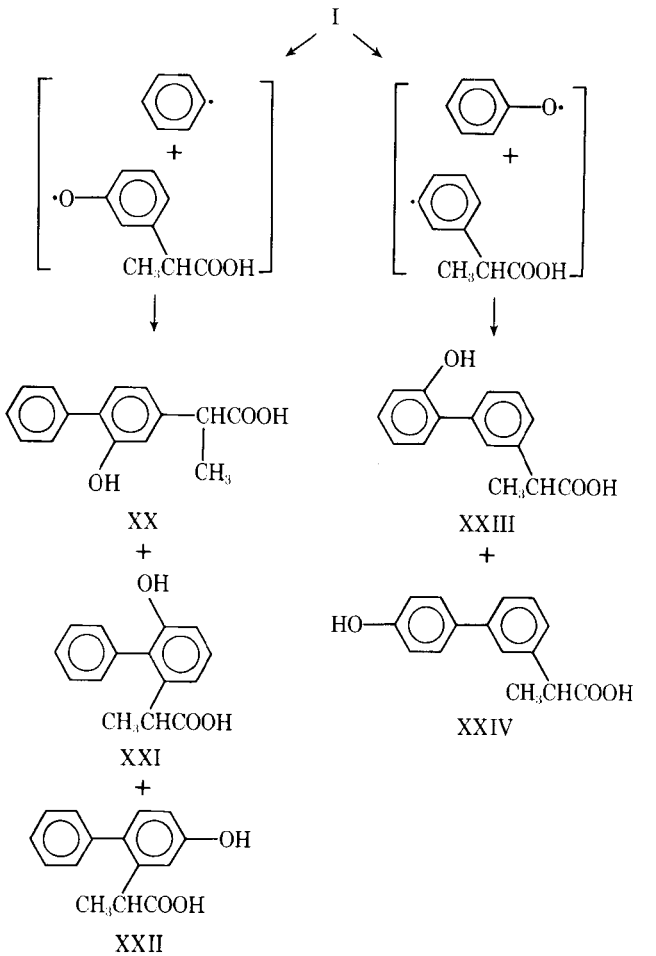
Figure 3 reveals the stability of stored samples by the unchanged characteristic endotherms. By comparison, the incompatibility of fenoprofen sodium dihydrate with propoxyphene hydrochloride was apparent, since mixtures became viscous oils after only a few hours of storage. Although somewhat more compatible with propoxyphene napsylate, fenoprofen sodium did interact over short periods (Fig. 4).

Thermal analyses of mixtures of fenoprofen calcium dihydrate with codeine sulfate pentahydrate indicated compatibility. The endotherm at 80° (Fig. 5) suggests the volatilization of the water of hydration of codeine sulfate pentahydrate; the endotherm at 105° is due to the volatilization of the water of hydration of fenoprofen calcium dihydrate; and the endotherm at 190° is a eutectic melt of the anhydrous components. This result is verified by the simultaneous differential thermal and thermal gravimetric analysis data in Fig. 7. Storage at room temperature did not alter the physical integrity of the mixture. However, thermograms reveal that the water of hydration of codeine sulfate was lost when stored at 50° for 1 week (Fig. 5).

The relative constancy of the eutectic melt of 190° suggests no interaction even when water was lost. Interaction of fenoprofen sodium dihydrate with codeine sulfate pentahydrate was visually apparent after a few hours. A crystalline, anhydrous, nonhygroscopic form of fenoprofen sodium might be compatible with propoxyphene or codeine salts. However, such a form could not be prepared, and the amorphous form is hygroscopic.

Thus, from a pharmaceutical point of view, fenoprofen calcium is clearly superior to fenoprofen sodium. Bioequivalence has been shown (2) by comparable blood levels from either fenoprofen calcium or fenoprofen sodium in similar oral dosage formulations.

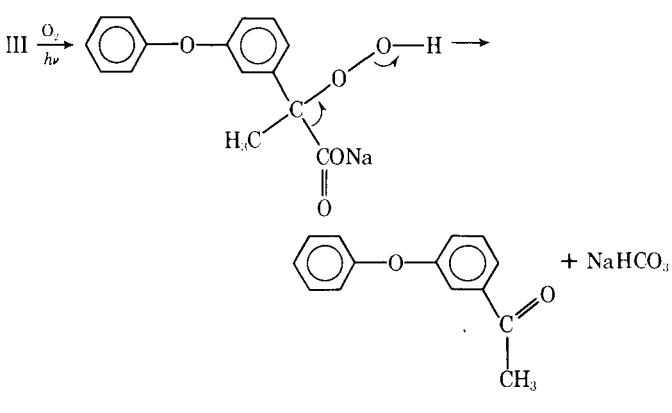
Sodium and calcium salts of fenoprofen are basic salts and, therefore, potentially reactive toward acids or acidic salts. Otherwise, fenoprofen has no particularly labile functional groups prone to alteration in typical pharmaceutical formulations. Routine preformulation stability studies




*Scheme I*

with the sodium and calcium salts revealed no significant degradation in the presence of formulative adjuncts.

However, aqueous solutions of fenoprofen sodium exposed to high-intensity short wavelength UV light[8] degraded slowly, but significantly, to several compounds more polar than fenoprofen, as shown by TLC ($R_f$ values given under *Experimental*). Major degradation products, A ($R_f$ 0.32) and B ($R_f$ 0.21), were isolated by column chromatography and characterized by IR, NMR, and mass spectrometry. Both compounds gave mass spectra virtually identical to the spectrum of fenoprofen, *i.e.*,




XXV

*Scheme II*

a molecular ion of *m/e* 242 and the major fragment of *m/e* 197. NMR spectra were similar in proton count and splitting patterns to fenoprofen. However, whereas fenoprofen has one deuterium-exchangeable proton, these compounds both exchanged two protons. Furthermore, IR spectra showed the presence of hydroxyl and carboxyl groups.

The same degradation was observed when isopropyl alcohol solutions of fenoprofen acid were exposed. These data provided strong evidence that fenoprofen had undergone a photochemically induced Claisen rearrangement as shown in Scheme I. Photo-Claisen rearrangements of diphenyl ethers have been studied (15, 16). The products isolated in the present study are two of the five possible isomeric α-methyl(phenyl)-hydroxybenzeneacetic or α-methyl(hydroxyphenyl)benzeneacetic acids (XX–XXIV). Comparison of UV spectra of A and B with *o*- and *p*-phenylphenols indicates that A is either XX or XXIII and that B is either XXII or XXIV[11]. No effort was made to identify the specific isomers by unambiguous synthesis.

To determine the relevance of such degradation to product stability, solutions of fenoprofen were exposed to both a carbon-arc lamp and direct sunlight. Prolonged exposure caused no detectable photo-Claisen rearrangement in either experiment. However, solutions exposed to the carbon-arc lamp formed trace amounts of *m*-phenoxyacetophenone (XXV), which was identified by comparison of spectral characteristics with an authentic sample. Although the mechanism is not certain, this ketone is most likely formed by hydroperoxide formation at the α-carbon followed by decarboxylation (Scheme II). However, GLC assays revealed that this mode of degradation was not quantitatively significant.

Direct sunlight exposure caused no detectable degradation when analyzed using TLC or mass spectrometry. Whereas the photo-Claisen mode of degradation can occur in the absence of oxygen but requires high energy irradiation, formation of the ketone requires oxygen. Neither reaction occurs to an extent that is detrimental to the product.

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