2, and was prolonged for up to 6 days. At pH 4, the release sustained for up to 12 days, and on increasing the pH to 7, the duration of the release increased to 22 days. Thus, it was also observed that as the pH increased, the solubility of the wall material decreased and the quantity of drug released per day decreased. When the pH was raised to 10, no dissolution of the polymer wall occurred and no release of secretin was observed for several days.

The data indicated that the drug was perhaps released by polymer dissolution at the polymer–water interface by a mechanism similar to that discussed previously (6, 7). Detailed study of this polymer will be necessary before the complete mechanism for erosion can be understood; the mechanism of release is the subject of further study. However, in the present study the interest was more on controlled release of the drug at low pH, which has been achieved. The above type of capsules would be suitable for sustained drug release at low pH. Further, since the polymer was erodible up to pH 8, it can form a suitable biosoluble wall material for encapsulating other drugs. The biocompatibility of this material is being studied.

Notable features of the microcapsules described in this report are: their ability to undergo surface erosion and, hence, release of the core material by zero-order kinetics, and sensitivity of the erosion rate to the surrounding aqueous environment (pH). A pH environment has a major effect on the erosion rate and, thus, controls the drug release which is increased by decreasing the pH.

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Reaction of Phenobarbital with Diphenhydramine

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Abstract □ A compound of low water solubility, consisting of phenobarbital–diphenhydramine in a 1:1 ratio and mp 109.5–110.5° was isolated from a prescription which had been dispensed as a clear solution and later returned with a white sediment. The information obtained suggested that it was either an easily dissociated complex or a salt.

Keyphrases □ Phenobarbital—reaction with diphenhydramine, complexation, salts □ Diphenhydramine—reaction with phenobarbital, complexation, salts □ Complexation—phenobarbital and diphenhydramine, salts

A number of salts, complexes, or addition compounds formed by barbiturates, particularly by phenobarbital, have been recorded previously (1–6). Similarly, there are recorded complexes and salts for diphenhydramine, the best known being dimenhydrinate, USP (7). The products formed by heating diphenhydramine and barbital or allobarbital in alcohol at 100–120° are reported to be 1:1 salts melting at 86 and 102–103°, respectively (8).

Literature pertaining to intravenous admixtures refers to diphenhydramine hydrochloride as being incompatible with phenobarbital sodium (9–11) as well as several other barbiturate salts; forming particulate matter (12, 13), forming a precipitate (14), or as not remaining clear for 24 hr after mixing (15). The only explanation provided is that solutions of sodium barbiturates and sodium diphenylhydantoin are alkaline and may lead to the formation of precipitates from solutions of acid salts. A previous study (16) pointed out that aqueous solutions of diphenhydramine hydrochloride and phenobarbital sodium will form a precipitate when mixed in low concentrations, even at pH values at which phenobarbital would be soluble. It was assumed that the precipitate was an undissociated, less soluble diphenhydramine–phenobarbital complex. No characteristics for this substance were reported.

The reported compound was first obtained from the crystalline settlement in a compounded prescription consisting of 250 ml of diphenhydramine hydrochloride elixir in which 750 mg of phenobarbital sodium had been dissolved in accordance with physician's instructions. When prepared, the mixture slowly became cloudy and then deposited crystals over several days. Upon filtration and recrystallization of the solid from ~75% alcohol, the hard, colorless crystals melted at 109.5–110.5° (uncorrected). The product was found to be composed of phenobarbital–diphenhydramine (1:1).

The formation of the crystals could be avoided by dissolving the equivalent amount of phenobarbital in 10 ml of alcohol and mixing it into the elixir. Such a sample was still free of crystals after 1 year. Since the crystals are very soluble in alcohol, somewhat soluble in water, and the pH of the elixir results in only a low concentration of diphenhydramine base, the product probably does not form in an amount sufficient to exceed its solubility in the hydroalcoholic medium.

EXPERIMENTAL

Diphenhydramine hydrochloride elixir[1], diphenhydramine[1], diphenhydramine hydrochloride[1], phenobarbital[2], and phenobarbital sodium[2] were obtained as indicated. The various solvents were USP or reagent grade.

[1] Elixir Benadryl, Parke-Davis & Co.; the diphenhydramine and its hydrochloride were provided by Parke-Davis & Co.

[2] Merck & Co., Rahway, N.J., commercial packages.

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The sample of diphenhydramine hydrochloride elixir had a pH of 6.8, which changed to 8.35 when 750 mg of phenobarbital sodium was dissolved in 250 ml of the sample. The mixture slowly became turbid, cleared as some oily droplets formed, and eventually crystallized over a period of several days. A crop of 833 mg of slightly pink crystals was collected. After treatment with charcoal and several crystallizations from ~30% alcohol, long, colorless needles, mp 109.5–110.5° (uncorrected)[3], were obtained. From 75–95% alcohol, clear, dense prisms of the same melting point were obtained. The crystals were dried *in vacuo* over phosphorus pentoxide at 80°.

Anal.—Calc. for $C_{29}H_{33}N_3O_4$: C, 71.45; H, 6.82; N, 8.62. Found[4]: C, 71.22; H, 6.77; N, 8.73.

After removal of the first crop of crystals, the filtrate was concentrated on a steam bath and then allowed to stand in open air. Large crystals formed (probably some sucrose since the elixir contains considerable syrup) and the mixture was extracted with three portions of ether. After removal of the ether the residue was taken up in 95% alcohol, treated with charcoal, and filtered. An additional 168 mg (mp 108–110° and giving no depression of melting point with previous crystals) of clear prisms was obtained, representing an overall yield of 95.9% based on the diphenhydramine hydrochloride present.

RESULTS AND DISCUSSION

The crystalline product from diphenhydramine hydrochloride elixir is easily soluble in 95% alcohol and is soluble in ether, acetone, chloroform, hot benzene, and somewhat soluble in water.

The same crystalline product could be obtained by dissolving phenobarbital in diphenhydramine with warming, followed by solution of the clear viscous material in alcohol. On cooling, prisms formed with mp 108–109°.

When a solution of 714 mg of phenobarbital in 10 ml of 95% alcohol was added to 240 ml of diphenhydramine hydrochloride elixir, the mixture remained clear and free of crystals for 1 year. There was no change in pH when the solution of phenobarbital was mixed with the elixir. It is probable that the small increase in alcohol concentration coupled with the low dissociation of the diphenhydramine hydrochloride in acid medium may not allow enough compound to form to exceed the solubility.

A solution of 300 mg of diphenhydramine hydrochloride in 30 ml of water had a pH of 5.5. When 261 mg of phenobarbital sodium was added with stirring, the mixture immediately became turbid. Droplets settled out, which quickly crystallized, and the pH changed to 7.5. After chilling, filtrating, washing, and drying, a crop of 425 mg (84.8%) of white crystals was obtained. The product melted sharply at 108–109° and gave no depression of melting point when mixed with material obtained from the prescription.

The UV spectra of phenobarbital, its sodium salt, diphenhydramine, its hydrochloride, and the product were compared, but no characteristics allowing distinction between a salt or a simple mixture could be observed. This agrees with observations reported for the phenobarbital–quinine complex (17).

A comparison of the IR spectra of potassium bromide pellets of phenobarbital, its sodium salt, diphenhydramine hydrochloride, and of the product indicated that the typical tertiary amine salt absorption at 2400–2700 cm^{-1} had disappeared in the product and the typical enolization band of phenobarbital (1620 cm^{-1}) is weak and shifted to ~1670 cm^{-1}. When the IR spectra of the product and of an equimolar mixture of phenobarbital and diphenydramine in chloroform were compared, no differences could be observed.

The NMR spectra of the product and an equimolar mixture of phenobarbital and diphenhydramine were run in deuterochloroform and compared. Most peaks were identical and could be assigned easily by comparison with spectra of the individual components. The only exception was a downfield signal (broad singlet accounting for two protons) which appeared at 10.9 ppm in the spectrum of the product and shifted upfield to 10.4 ppm in the spectrum of the mixture.

The sharp melting point of the product and the broad melting of mixtures [(102–147°) mixed with diphenhydramine hydrochloride and (106–155°) when mixed with phenobarbital] suggest that a new substance exists in the crystalline state. The evidence from the spectral measurements in solution indicates extensive dissociation.

[3] The melting points were obtained on a Hoover Melting Point Apparatus in open capillaries and are uncorrected. UV spectra were determined in 95% ethanol on a Beckman model DK-2A recording spectrophotometer. IR spectra were recorded either as potassium bromide pellets on a Beckman model 8 Infrared Spectrometer or in chloroform solution on Beckman model IR-33 Spectrometer. NMR spectra were recorded in deuterochloroform in a Varian model EM-360 Spectrometer using 1% tetramethylsilane as an internal reference standard.

[4] Spang Microanalytical Laboratory, Ann Arbor, Mich.

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