Increased Dissolution Rates of Water-Insoluble Cardiac Glycosides and Steroids *via* Solid Dispersions in Polyethylene Glycol 6000

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Abstract □ Dissolution rates of water-insoluble drugs such as digitoxin, 17-methyltestosterone, hydrocortisone acetate, and prednisolone acetate were markedly increased when dispersed in polyethylene glycol 6000. In addition, a supersaturation of each drug could be quickly attained when an excess amount of drug was studied. The increased dissolution rate was believed to be attributed to the molecular and/or the colloidal dispersion of the drug in the matrix of polyethylene glycol 6000.

Keyphrases □ Dissolution rates—digitoxin, 17-methyltestosterone, hydrocortisone acetate, prednisolone acetate solid dispersions □ Polyethylene glycol 6000 dispersions—increased dissolution rates of water-insoluble glycosides, steroids □ Digitoxin–polyethylene glycol 6000 solid dispersion—dissolution rate □ 17-Methyltestosterone–polyethylene glycol 6000 solid dispersion—dissolution rate □ Prednisolone acetate–polyethylene glycol 6000 solid dispersion—dissolution rate □ Hydrocortisone acetate–polyethylene glycol 6000 solid dispersion—dissolution rate □ Absorption, oral, fast release—polyethylene glycol–insoluble drug dispersions

From the consideration of effects of the molecular size, viscosity, and supercooling of polyethylene glycol polymers on the formation of fast-release solid dispersions, Chiou and Riegelman (1) recently predicted that these water-soluble polymers should be able to serve as universal carriers in increasing dissolution rates and oral absorption of poorly water-soluble or water-insoluble drugs. Although the exact physical nature has not been fully studied, the *in vitro* dissolution rate of griseofulvin, an insoluble antifungal antibiotic, was shown to increase markedly when solid dispersed in polyethylene glycol 4000, 6000, and 20,000 (1). More encouragingly, the absorption rates and total availability of griseofulvin dispersed in polyethylene glycol 6000 after oral administration to dogs (2) and man (3) were much faster and higher as compared to commercially available, micronized products. The dissolution characteristics of four additional, insoluble drugs dispersed in polyethylene glycol 6000 are discussed in this communication to substantiate further the contention concerning the universality of utilization of polyethylene glycol polymers as matrix carriers.

EXPERIMENTAL

Materials—The following were used: hydrocortisone acetate, reagent grade[1]; 17-methyltestosterone, reagent grade[2]; prednisolone acetate, reagent grade[3]; digitoxin, USP grade, microcrystalline[4]; and polyethylene glycol 6000[5]. Except for polyethylene glycol 6000, powders of the drugs all passed through a 200-mesh sieve.

Preparations of Solid Dispersion—Physical mixtures of polyethylene glycol 6000 and insoluble drugs were heated with stirring in an oil bath until completely melted. Clear and colorless melts were then poured onto a stainless steel plate and allowed to solidify by natural cooling. After several days of standing in the desiccator, solid masses were powdered, and an 80–200-mesh fraction was then collected for the dissolution-rate studies.

Table I—Twenty, Fifty, and Seventy Percent Dissolution Times for Selected Drugs in Various Physical Forms in Half-Saturation Dissolution Test

Preparations	T_{20}, min.	T_{50}, min.	T_{70}, min.
Pure prednisolone acetate[a]	8.0	45.0	—
Fused mixture of prednisolone[a] acetate–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	~0.6
Pure 17-methyltestosterone	2.0	12.0	28.0
Fused mixture of 17-methyltestosterone–polyethylene glycol 6000 (5:95 w/w)	≪1.0	≪1.0	~0.6
Pure hydrocortisone acetate	20.0	—	—
Fused mixture of hydrocortisone acetate–polyethylene glycol (5:95 w/w)	≪1.0	≪1.0	1.5
Pure microcrystalline digitoxin	15.0	80.0	—
Fused mixture of digitoxin–polyethylene glycol 6000 (2:98 w/w)	≪1.0	≪1.0	0.3–0.5

[a] This test system utilized only 30% saturation.

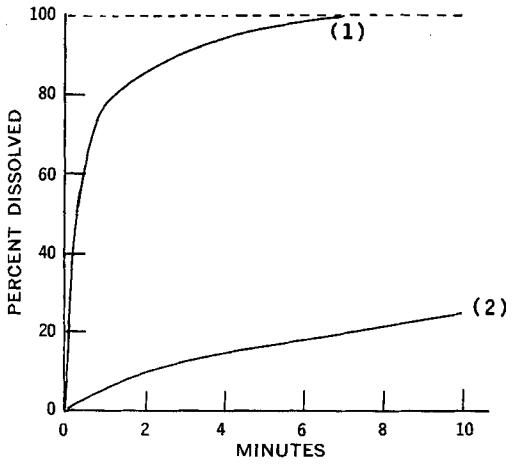

Figure 1—*Dissolution-rate studies of prednisolone acetate, 2.5 mg./500 ml. water, at 25°. Key: (1), 5% prednisolone acetate–polyethylene glycol 6000; and (2), pure prednisolone acetate powder.*

[1] Merck Sharpe & Dohme Research Laboratory, West Point, Pa. (lot No. 09C0017).
[2] J. T. Baker Chemical Co., Phillipsburg, N. J. (lot No. 5-4900).
[3] The Upjohn Co., Kalamazoo, Mich. (lot No. U-5955).
[4] C. G. Boehringer and Suthne G.b.H., Mannheim, Germany (lot No. 65618).
[5] Carbowax 6000, Union Carbide Co.

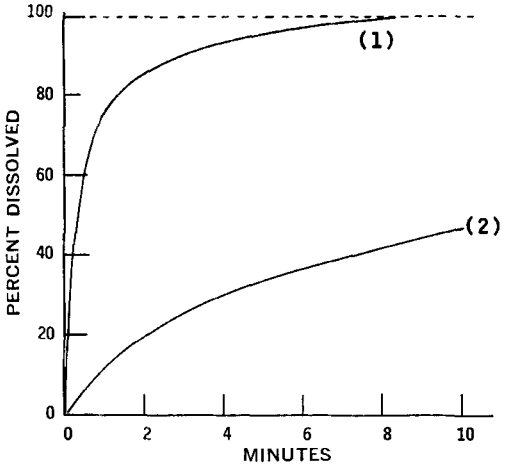

Figure 2—*Dissolution-rate studies of 17-methyltestosterone, 8 mg./500 ml. water, at 25°. Key: (1), 5% 17-methyltestosterone–polyethylene glycol 6000; and (2), pure powder.*

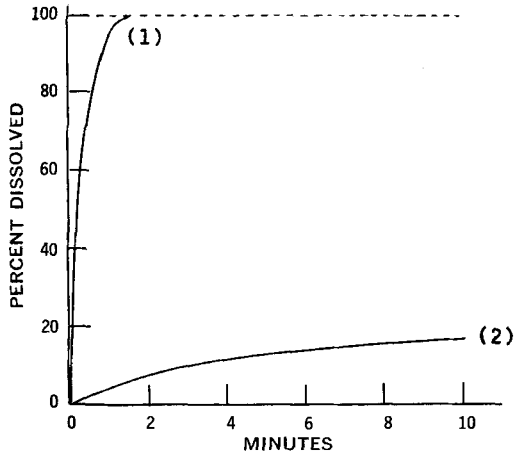

Figure 4—*Dissolution-rate studies of digitoxin. 3.5 mg./500 ml. water, at 25°. Key: (1), 2% digitoxin–polyethylene glycol 6000; and (2), microcrystalline pure powder.*

Stability Studies of Fused Mixtures—To test whether the drugs were decomposed by the fusion process, UV spectral and TLC characteristics of the pure and the processed samples were studied. In the UV study, the spectra of the pure and the dispersed drugs in the 1% ethanol solutions were scanned from 340 to 200 nm. by the recording Beckman DB spectrophotometer. Ethanol solutions of pure and dispersed drugs were spotted on the thin-layer plate and developed in the solvent system of chloroform–ether–methanol (6:3:1 v/v). The plates were sprayed with 20% sulfuric acid and heated at 110° for 1 hr.

Dissolution-Rate Studies—Dissolution rates of the pure and dispersed drugs were studied in 500 ml. distilled water at room temperature. The apparatus and the procedure were similar to those previously described (1). Two different amounts of drugs were used, one equivalent to 50% (30% in the case of prednisolone acetate) the amount that dissolves in 500 ml. water and one equivalent to three times (1.8 times in the case of prednisolone acetate) the saturated solubility if all dissolves. The solubility of each drug in 100 ml. of water at 25° is as follows: 1.0 mg. for hydrocortisone acetate (4), 3.2 mg. for methyltestosterone (4), 1.4 mg. for digitoxin (estimated in this laboratory), and 1.7 mg. for prednisolone acetate (estimated in this laboratory).

The wavelengths used for measuring optical absorbance in the dissolution-rate studies were as follows: 250 nm. for the hydrocortisone acetate, 17-methyltestosterone, and prednisolone acetate, and 220 nm. for digitoxin. In the study of the higher concentration of 17-methyltestosterone, 215 nm. (minimum absorbance) was used. The concentration of drugs was calculated according to established Beer's law plots. The presence of the carrrier in this study did not affect the assays. All studies were run at least in duplicate. The dissolution characteristics of the solid dispersions were reproducible, with only negligible variation between runs. A slightly larger but relatively insignificant variation was seen between runs of the pure compounds.

RESULTS AND DISCUSSION

Stability Studies—UV spectra and molar extinction coefficients of the pure and processed drugs were identical within experimental error, indicating the lack of decomposition; a single spot with the same R_f value was found for both the pure and processed compounds on the thin-layer plates. However, the sample of the processed digitoxin showed two additional spots, one slightly darker and one lighter than the spot of pure digitoxin. This result probably indicates some decomposition of digitoxin after the fusion process, although it could not be detected by the UV spectra. Digitoxin might be protected from decomposition by lowering the fusion temperature (170° used in this study), decreasing the proportion of digitoxin in the solid dispersion, or using the solvent method. Further investigation of this aspect should be undertaken.

Dissolution-Rate Studies—Table I and Figs. 1–4 summarize the strikingly enhanced dissolution rates obtained by the dispersion systems when the half-saturation dissolution test was utilized. The time required to dissolve 50% (designated by T_{50}) of the four insoluble drugs was much less than 1 min., and the time required to dissolve 70% (designated by T_{70}) was also less than 1 min. with the exception of hydrocortisone acetate (1.5 min.). Furthermore, all the drugs dissolved completely in less than 8 min.

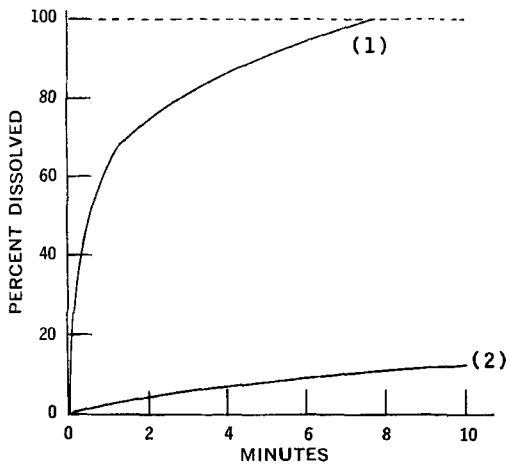

Figure 3—*Dissolution-rate studies of hydrocortisone acetate, 2.5 mg./500 ml. water, at 25°. Key: (1), 5% hydrocortisone acetate–polyethylene glycol 6000; and (2) pure powder.*

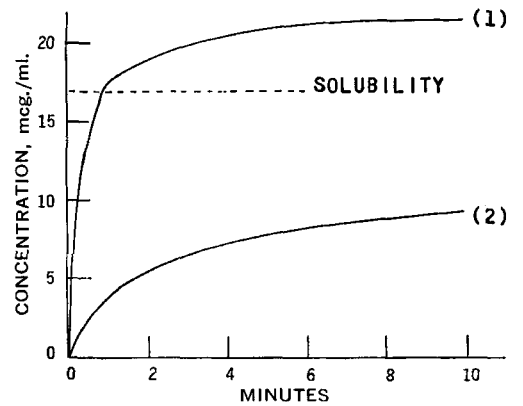

Figure 5—*Dissolution-rate studies of prednisolone acetate, 15 mg.-500 ml. water, at 25°. Key: (1), 5% prednisolone acetate–polyethylene glycol 6000; and (2), pure powder.*

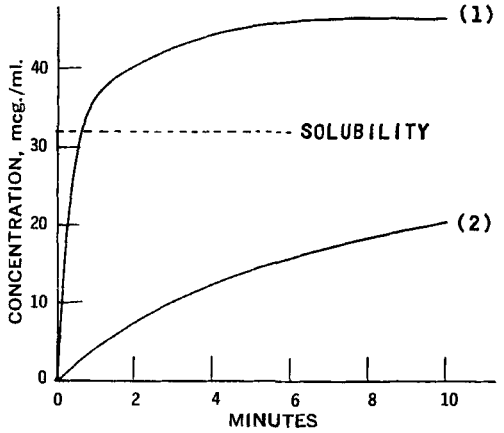

Figure 6—*Dissolution-rate studies of 17-methyltestosterone, 48 mg./500 ml. water, at 25°. Key: (1), 5% 17-methyltestosterone–polyethylene glycol 6000; and (2), pure powder.*

The dissolution from the conventional or microcrystalline (digitoxin only) powders was much slower. T_{20} ranged from 2 to 20 min., and T_{50} ranged from 12 to 80 min. When the supersaturated dissolution test method was utilized, all drugs in the dispersed systems reached supersaturation in less than 1 min. (Figs. 5–8). The fast dissolution and the attainment of supersaturation of all four drugs dispersed in polyethylene glycol 6000 are similar to what were previously reported for griseofulvin (1). Although the exact physical nature of these dispersed systems was not investigated in this preliminary study, it is believed that the reduction of the particle size of the drug to the molecular and/or colloidal level is the primary contributing factor for these striking phenomena. This belief is based on the theoretical considerations of: (*a*) molecular size difference between the polymer and the drug, and (*b*) supercooling and viscous effect of the drug–polyethylene glycol melt (1). Other possible contributing factors, such as solubilization due to the formation of soluble complexes with the polymer and the polymorphic form of the drug pres-

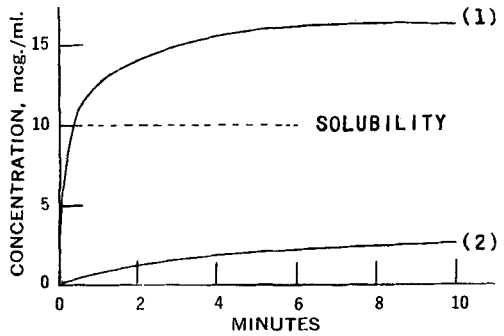

Figure 7—*Dissolution-rate studies of hydrocortisone acetate, 15 mg./500 ml. water, at 25°. Key: (1), 5% hydrocortisone acetate–polyethylene glycol 6000; and (2), pure powder.*

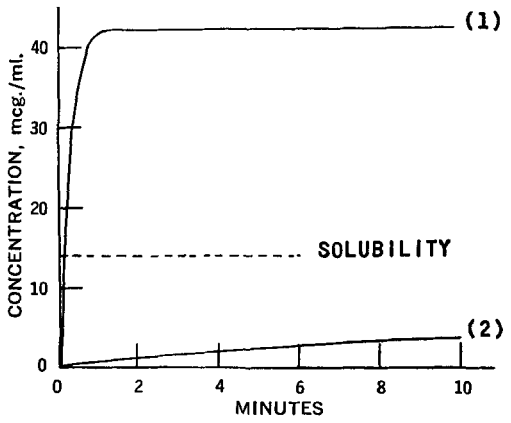

Figure 8—*Dissolution-rate studies of digitoxin, 21 mg./500 ml. water, at 25°. Key: (1), 2% digitoxin–polyethylene glycol 6000; and (2), pure microcrystalline powder.*

ent in the dispersion form, remain to be explored. The dissolution study for the fused pure drugs was not performed because of their decomposition after melting. Their melting points are much higher than the temperatures used to prepare the drug–polyethylene glycol melts.

From evidence in this and previous studies, one can justify the universality of the polyethylene glycol polymers to serve as fast-release carriers for poorly soluble drugs. Although griseofulvin has been shown to increase absorption in both man and dogs by dispersing in polyethylene glycol 6000, it appears that this type of system may have application to enhance absorption of poorly soluble drugs that can be incorporated into these systems without decomposition.

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