Dissolution, Stability, and Absorption Characteristics of Dicumarol in Polyethylene Glycol 4000 Solid Dispersions

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Abstract □ The dissolution characteristics of dicumarol were markedly enhanced by preparing dispersions of drug in polyethylene glycol 4000. Solid dispersions of varying weight fractions were formed by a melt method without measurable drug degradation or evaporation. There were no significant differences in dissolution rates among weight fractions, with dynamic solubilities being ~2.5 times greater than dicumarol's equilibrium solubility. No indications of drug polymer complexation were noted from equilibrium or *in situ* absorption experiments. Incorporation of solid dispersions into direct compression tablets provided dosage forms with fast-release properties relative to test tablets of physical mixtures and a commercially available product. Percentages dissolved in 30 min were 370% greater for 1:3 and 1:5 (w/w) solid dispersion tablets compared to a commercial tablet at 37° with a pH 7.5 dissolution buffer. X-ray diffraction of test powder revealed that the crystalline nature of the drug had altered during fusion preparation. Dissolution traits and drug stability for solid dispersions were maintained over 1 year of storage.

Keyphrases □ Dicumarol—dissolution, stability, and absorption characteristics in polyethylene glycol 4000 solid dispersions □ Dissolution—dicumarol in polyethylene glycol 4000 solid dispersions □ Polyethylene glycol 4000—effect on dicumarol dissolution, stability, and absorption

The preparation of drug–polymer disperions by fusion and solvent techniques has successfully increased dissolution properties (1–8) and bioavailability (5, 6, 9–12) of poorly water-soluble drugs. Properties of water-soluble polymers such as large molecular size, high viscosity, and supercooling can provide a dispersed drug in a metastable or fast-release form (1, 2). Povidone has been a popular choice as an inert carrier for dispersions prepared by solvent or coprecipitation methods. Among several examples, griseofulvin (3), sulfathiazole (4), and reserpine (5, 6) demonstrate faster dissolution rates when they are dispersed in povidone by a solvent method. For the fusion or melt method, polyethylene glycols have been employed extensively. The dissolution of prednisolone, methyltestosterone, hydrocortisone, and digitoxin has been enhanced by polyethylene glycol fusion dispersions (7). Similarly, enhanced dissolution rates of griseofulvin (2, 8), nitrofurantoin, ethotoin, and coumarin (13) in polymer melt systems were reported.

The oral anticoagulant dicumarol, 3,3′-methylene-bis[4-hydroxycoumarin], is practically insoluble in water (14). It is reported to be poorly and erratically absorbed from both powder and tablet dosage forms (15–17). The bioavailability of dicumarol in tablets is influenced by the type and amount of excipients (18). This drug's classification as dissolution rate limited was supported in studies in dogs (19) where a strong relationship between dissolution data and bioavailability and prothrombin time was noted.

Reports of poor and erratic bioavailability serve as a stimulus for examining new dicumarol formulations that may provide more complete and consistent absorption. The present investigation reports the preparation of dicumarol and polyethylene glycol 4000 solid dispersions by a fusion method and discusses possible mechanisms for their fast-release properties.

EXPERIMENTAL

Preparation of Test Powders—Solid dispersions of polyethylene 4000[1] and dicumarol[2] were prepared from physical mixtures by the fusion or melt method. Physical mixtures representing drug to polyethylene glycol 4000 ratios of 1:1, 1:3, and 1:5 (w/w) were heated over a thermostatic plate with constant stirring until a clear homogeneous melt was obtained. Melts were quickly poured on air-cooled aluminum pans or were glass-suspended in a vented hood. After 1 hr, solidified dispersions were stored in a desiccator for 2 days prior to pulverization.

Other physical mixtures containing heated drug and polymer were obtained by separately heating each component to 280° and then cooling and storing as described for dispersions. Particle-size reductions of physical mixtures were performed by a ball mill while reductions for solid dispersions and heated physical mixtures were accomplished by light tituration in a cooled mortar. Test powders were modified by sieving to provide particle sizes of 100–60 mesh for dispersions and physical mixtures and of <140 mesh for dicumarol.

Stability Testing of Physical Mixtures and Solid Dispersions—Assessments of dicumarol stability were conducted by UV spectroscopy, paper chromatography, and TLC. Alkaline solutions (0.1 *N* NaOH) prepared from powders and tablets were utilized in a paper separation with acetic acid–benzene–water (2:2:1) as a solvent (20) as well as for two thin-layer separations on silica gel plates[3] with fluorescent indicator[3]. Thin-layer solvent systems included 3 *M* ammonium hydroxide–ethyl acetate (1:1) and ether–chloroform–acetone (60:30:1). Additional separations were performed with solutions prepared by redissolving dicumarol precipitates obtained from acidified samples.

In chromatographic experiments in which [^{14}C]dicumarol[4] was incorporated into solid dispersions, silica gel plates were scraped in sections following development. The radioactivity of each scraping was determined by suspending each in cocktail[4] and counting with the aid of a liquid scintillation counter[5]. All samples were corrected for quenching by quench curves.

Nonequilibrium Solubility Studies—Powder dissolution testing was conducted with a 1000-ml, three-necked, round-bottom flask containing 700 ml of 0.05 *M* phosphate buffer (pH 7.5). The apparatus was maintained at 37.0 ± 0.5° by a water bath. To mix the medium, a sleeve stirrer positioned 4 cm from the flask bottom was connected to a constant-speed motor adjusted to 60 rpm. Test powders containing 100-mg equivalents of dicumarol were added to the medium at time zero followed by 4-ml sampling with replacement. Samples were immediately filtered with 0.05- or 0.22-μm filters[6], and absorbance values were obtained at 314 nm[7] for each sample before and following pH adjustment to 12 with 4 *N* NaOH. Amounts dissolved were calculated from standard curves in pH 7.5 and 12.0 media and corrected for sample dilution (21).

Preparation of Test Tablets—After storage of test powders for periods not exceeding 2 weeks, portions of physical mixtures and solid

[1] City Chemical Corp. New York, N.Y.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] Eastman Kodak Co., Rochester, N.Y.
[4] Amersham-Searle, Arlington Heights, Ill.
[5] LS-150, Beckman Instruments, Fullerton, Calif.
[6] Millipore Corp., Bedford, Mass.
[7] Model 100-60, Hitachi Ltd. Tokyo, Japan.

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dispersions were combined and blended with anhydrous lactose[1]. The diluent was added to provide tablets of equal weight, 325 mg. To most formulations, 1% magnesium stearate[1] was added to minimize capping. Formulations were prepared as direct compression tablets with the aid of a single-punch tablet press[8]. Compression force was adjusted to give tablets of comparable hardness (4.4 ± 0.6 kg). Tablet lots were tested for hardness[9], content uniformity, thickness, dissolution, stability, and weight variation.

Tablet Dissolution Studies—The tablet dissolution apparatus, comprised of a beaker and basket arrangement, was maintained at 37.0 ± 0.5° by a water bath. The dissolution medium consisted of 1000 ml of deaerated, 0.05 *M* phosphate buffer (pH 7.5). Studies were conducted with test tablets and a selected commercial product. At frequent time intervals after immersion of the baskets, which were rotated at 50 rpm, 4.0-ml samples were withdrawn. Samples were filtered and treated as described for powder nonequilibrium studies.

Absorption from *In Situ* Intestinal Loops—Male Sprague-Dawley rats[10], 260–300 g, were fasted 24 hr prior to the procedure. After anesthetization with 40 mg of pentobarbital sodium[2]/kg ip, a midline incision was made. A 15-cm segment representing the upper jejunum was carefully cannulated and gently rinsed with warm saline to remove lumenal matter. Tubing was attached to each cannula and was then passed through a perfusion pump[11] leading to a reservoir. Perfusion was carried out in a recycling fashion with the 60 ml of drug containing buffer maintained at 37.0 ± 0.5° in the reservoir. The perfusion buffer was passed through the intestine in a proximal to distal direction at a calibrated rate of 4.8 ml/min. This rate provided rapid perfusion without overly distending the intestinal segment. Samples were taken from the reservoir, and amounts absorbed were corrected for fluid flux based on reservoir volume.

Dicumarol levels in perfusion samples were determined by a previously described method (17) as revised by Nagashima *et al.* (22).

Data Analysis—The amounts dissolved in powder and tablet dissolution studies were compared between preparations and sample times by one- or two-way analysis of variance and Tukey testing (23).

X-Ray Diffraction Studies—Test powders were firmly packed on a slide with glass windows. Diffraction spectra[12] were prepared by scanning at a rate of 2°/min in terms of a 2θ angle.

RESULTS AND DISCUSSION

Preparation and Stability Studies—The temperature required for obtaining melts of dicumarol with polyethylene glycol 4000 was below that of the pure drug, 290°, and measurably decreased as the weight fraction of polymer was increased. Lowering in melting points as a function of weight fraction for binary systems is not an unexpected or unique phenomenon (1, 24). For dicumarol–polyethylene glycol 4000 dispersions of 1:1, 1:3, and 1:5, melt temperatures necessary to obtain a visually clear, homogeneous liquid were 275, 263, and 255°, respectively. Dispersions of drug to polymer weight fractions of >1:1 (such as 2:1) could not be prepared at a temperature less than the drug's melting point. Smaller weight fractions were not considered appropriate based on results of powder dissolution studies.

Powdered and milled physical mixtures of 280° heated and unheated drug and polymer appeared white and crystalline, while melted dispersions were orange brown. Polarized light microscope examination indicated the presence of crystalline materials in dispersions and physical mixtures. The crystalline appearance of all physical mixtures, composed of heated and unheated components, resembled that of powdered dicumarol and polyethylene glycol while that of the melt dispersions was distinctly different. Fusion products contained smaller crystals of orange-like reflection dispersed in a clear polymer matrix.

The concern for possible drug degradation was emphasized by the coloration of fusion products and by other studies (7) demonstrating drug degradation in polyethylene glycol melts. Three chromatographic separations of ^{14}C-labeled dicumarol dispersions failed to show any degradation materials. Similar chromatographic studies performed with solutions of dispersion powders and direct compression tablets that had been stored for 1 year revealed lack of degradation or drug loss.

It was concluded from the stability tests that, at the temperature required for drug–polymer melts, drug decomposition did not occur and, thus, was not responsible for the coloration of the fusion dispersions. The heating temperature necessary to discolor polymer or drug separately exceeded the melt temperatures for fusion. The orange-brown coloration apparently is unique to the solid dispersion. Differences in color between dispersions obtained by melting without measurable drug degradation and their physical mixtures were reported (2).

Nonequilibrium Solubility Studies—Solubility experiments for comparing powder dissolution rates demonstrated a dramatic enhancement in initial dicumarol solubility for the three dispersions (Fig. 1). Physical mixtures of heated materials gave similar release profiles to those of other physical mixtures and powdered drug. As summarized in Table I, the maximum observed solubility for dispersions over the 23-hr studies was approximately twofold greater than that of the physical mixtures, with maximum levels for dispersions noted at 60 min compared to >660 min for physical mixtures and pure drug.

Among the three weight fractions, significant differences in the amounts of dicumarol dissolved were not found at any sampling interval. Large variability in the initial amounts released by the dispersion appeared to mask any small differences that might exist between the prepared weight fractions. At the end of 23 hr, final dicumarol concentrations for all dispersions were 30% greater than dicumarol powder or dicumarol powder incorporated into physical mixtures. Comparisons of the percentage dissolved by time showed the drug levels to be constant for all dispersions for 8–23 hr. Whether dicumarol's solubility in the media of solid dispersion preparation approaches that of pure drug after 23 hr was not examined.

The supersaturated state of the media created by the solid dispersions represented a dissolution of <40% of the drug initially added to the system, thereby maintaining solid drug in excess throughout the experiments. Amounts dissolved in 10 min were eightfold greater for dispersions compared to powdered pure drug. Drug levels fell rapidly after 60 min for all dispersions, providing profiles that might be expected for a high energetic drug form (5, 25–28). The ratio of dynamic to equilibrium solubility for dicumarol dispersions was ~1.4 for all weight fractions, while the ratio of the dynamic solubility for dispersions relative to the equilibrium solubility for dicumarol powder was 2.5. Upon standing, drug crystallization and loss in UV absorbance were noted in withdrawn dissolution samples. To obtain solubility values accurately, it was necessary to filter and obtain absorbance measurements immediately.

UV spectra and calculations of amounts dissolved for alkalinized and nonalkalinized filtered samples from respective standard curves seemed to confirm the existence of a supersaturated state in the early time periods. Filtration of samples through 0.45–0.05-μm filters did not alter measured drug concentrations. A similar dissolution characteristic was described (28) for polymorphs of cortisone acetate. Another mechanism for describing the overshoot of equilibrium concentration during initial dissolution periods was proposed earlier (29). By this explanation, drug release from a polymer mixture continues after saturation as a result of further dissolution of drug in complex with polymer, which acts as a drug carrier.

The similarity of drug release for pure drug compared to physical mixtures demonstrates the relative noninteractive nature of drug and polymer such that wetting and complexation features of polyethylene glycol may be negligible in this dispersion system. Wetting effects may explain the slightly faster initial dissolution rates of physical mixtures compared to drug powder. Observations of higher equilibrium solubilities for the dispersion and the possible participation of the polymer as a

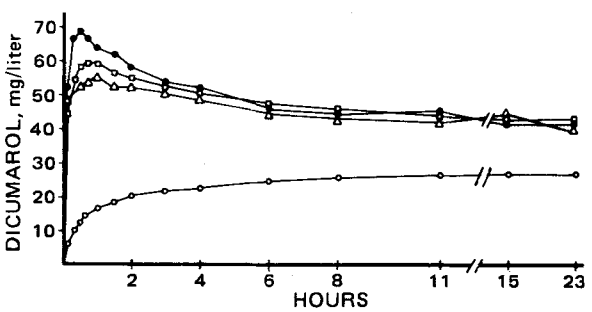

Figure 1—*Dissolution of dicumarol test preparations at 37°. Key:* ○, *dicumarol powder;* □, *1:1 (w/w) dicumarol–polyethylene glycol 4000 dispersion;* ●, *1:3 (w/w) dicumarol–polyethylene glycol 4000 dispersion; and* △, *1:5 (w/w) dicumarol–polyethylene glycol 4000 dispersion.*

[8] Stokes model F, Pennsalt Chemical Corp., Warminster, Pa.
[9] Stokes hardness testers, Pennsalt Chemical Corp., Warminster, Pa.
[10] Southern Animal Farms, Prattville, Ala.
[11] Harvard Apparatus Co., Millis, Mass.
[12] Philips X-ray diffraction unit type 12215/0.

Table I—Summary of Dissolution and Equilibrium Solubility for Dicumarol Test Powders

Preparation	t_{max}, min	Dynamic Solubility, mg/liter	Concentration, mg/liter 10 min	40 min	1380 min
Dicumarol powder	>660	27.7 (0.6)[a]	6.3 (2.1)	14.9 (1.7)	27.3 (0.6)
Physical mixtures					
1:5 (w/w)[b]	>660	27.6 (1.4)	14.9 (1.9)	19.0 (2.9)	27.6 (1.0)
1:5 (w/w), heated[c]	>660	26.7 (2.7)	10.1 (0.9)	18.3 (3.9)	24.9 (1.7)
Solid dispersions					
1:1 (w/w)	40	59.4 (4.3)	44.6 (7.5)	59.4 (4.3)	41.6 (0.4)
1:3 (w/w)	30	69.3 (4.7)	54.0 (5.4)	67.4 (6.6)	41.6 (6.6)
1:5 (w/w)	60	54.9 (10.0)	49.0 (9.5)	53.1 (8.7)	41.4 (3.1)
Dicumarol powder with polyethylene glycol dissolution medium[d]					
0.071%	>660	25.6 (1.1)	5.9 (2.1)	11.7 (1.6)	26.7 (0.9)
0.043%	>660	25.4 (1.4)	7.5 (1.8)	14.7 (3.0)	25.0 (1.3)
0.014%	>660	27.3 (1.6)	9.1 (1.5)	14.4 (1.3)	26.3 (1.7)

[a] Mean ±*SD*; $n = 6$. [b] Dicumarol–polyethylene glycol 4000 (w/w). [c] Drug and polymer heated separately to 280° and cooled prior to preparation of physical mixture. [d] Concentration of polyethylene glycol 4000 in dissolution medium.

Table II—Summary of Tablet Dissolution Studies of Solid Dispersions, a Physical Mixture, and a Commercial Tablet of Dicumarol

Preparation	$t_{10\%}$	Percent Dissolved 10 min	30 min	60 min	90 min
Commercial	13.5	4.1 (0.4)[a]	15.0 (1.0)	19.4 (2.4)	22.2 (4.2)
Physical mixture, 1:5	31.0	4.7 (4.1)	10.2 (8.1)	12.5 (9.4)	13.0 (8.5)
Solid dispersions					
1:1[b]	7.1	15.5 (2.3)	46.6 (2.4)	57.2 (1.8)	73.8 (3.2)
1:3[b]	3.4	35.0 (5.1)	67.1 (2.2)	72.8 (1.7)	74.3 (3.1)
1:5[b]	3.1	38.2 (2.0)	72.8 (3.1)	78.1 (3.6)	79.0 (3.1)
1:5 without magnesium stearate[b]	2.2	48.4 (0.8)	70.7 (2.1)	76.0 (3.2)	77.3 (2.8)
1:1 polyethylene glycol 4000 medium[b]	5.6	17.8 (2.6)	52.0 (3.1)	66.2 (5.2)	73.0 (6.3)
1:5, 1-year storage[b]	3.0	39.6 (2.6)	72.0 (2.6)	79.6 (2.4)	78.1 (2.8)
1:1, 1-year storage[b]	6.7	16.5 (1.6)	47.6 (2.2)	58.3 (1.5)	75.2 (2.5)

[a] Mean ± *SD*; $n = 6$. [b] Significantly ($p < 0.05$) greater amounts dissolved at all sampling periods compared to physical mixture or commercial product.

dissolution carrier presented a need to evaluate better any contributions that polymer and dicumarol complexation may have on the dispersion's performance. In addition, dicumarol was reported (30) to interact with povidone to form highly soluble complexes. With conditions identical to previous studies, polyethylene glycol was predissolved in the media at three concentrations corresponding to those expected for complete polymer dissolution in the dispersions. As summarized in Table I and Fig. 2, equilibrium solubilities after 6 hr were independent of polymer concentrations. Amounts released prior to 6 hr decreased slightly as the levels of polyethylene glycol increased, which may be the result of viscosity influences on release rate.

Neither milling, melting, nor separate heating of dicumarol or polyethylene glycol 4000 to a temperature exceeding that required for melts influences dissolution (Table I). Marked enhancement in dicumarol dissolution in prepared fusion dispersions apparently is unique to the fusion product and not secondary to the polymer effects or the results of applied temperature.

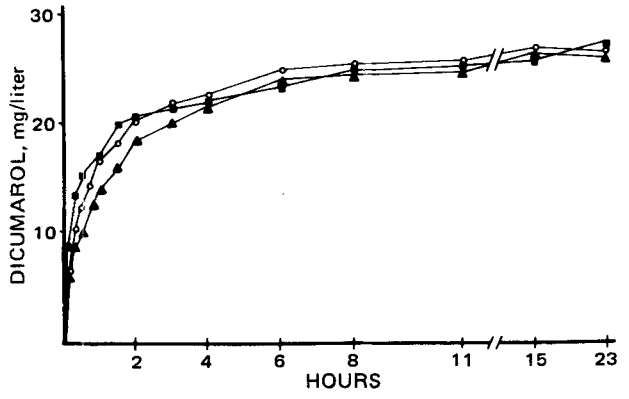

Figure 2—*Dissolution of dicumarol powder and physical mixture at 37°. Key: ○, dicumarol powder; ■, 1:5 (w/w) dicumarol–polyethylene glycol 4000 physical mixture; and ▲, dicumarol powder in 0.071% polyethylene glycol 4000 dissolution media.*

Since higher solubility of dicumarol in solid dispersions did not seem to be a consequence of polymer–drug complexation, the elevated drug levels during the latter portion of the equilibrium experiments may be the result of an inhibitory effect of the polymer on the drug's conversion to a stable, less soluble crystalline species. Prevention of nucleation and recrystallization to a stable crystalline form by solutions of high molecular weight polymers such as povidone was previously discussed (4, 5). In evaluating the influence of the drug–polymer dispersion ratio with respect to polymer medium concentration, retardation of stable crystal formation was independent of the polymer ratio. Therefore, the minimum inhibitory polymer levels appear to be <0.014% with 37° dissolution media.

Tablet Dissolution Studies—Solid dispersions and physical mixtures were incorporated into direct compression tablets to evaluate the effects of tableting on dicumarol release from solid dispersions and to provide a solid dosage form for future comparative bioavailability studies. Tablets were designed to be of equal weight by the addition of lactose and were nondisintegrating.

Results of tablet dissolution experiments expressed as percentage released are presented in Table II and Fig. 3. Calculation of dissolution rate constants through application of tablet dissolution models was considered inappropriate since previous nonequilibrium profiles revealed that observed release kinetics would be complex and reflective of both rapid release and crystallization. Comparisons of percentage dissolved at 5–90 min gave the rank order for the dissolution of test tablets containing 1% magnesium stearate as a lubricant: 1:5 = 1:3 >1:1 solid dispersions >1:5 physical mixture = commercial product.

Tablets containing the dispersions of 1:3 and 1:5 weight fractions showed marked increases in percentage released at 10, 30, 60, and 90 min compared to commercial and physical mixture forms with approximate increases of 290, 366, 290, and 245%, respectively. Dissolution profiles for tablets representing the three weight fractions stored for 1 year were identical to those for freshly prepared tablets. The markedly slower dissolution noted for the nondisintegrating tablet compared to previously examined powders indicates that this drug's dissolution may be further maximized by incorporating powdered dispersion into disintegrating tablets or capsules.

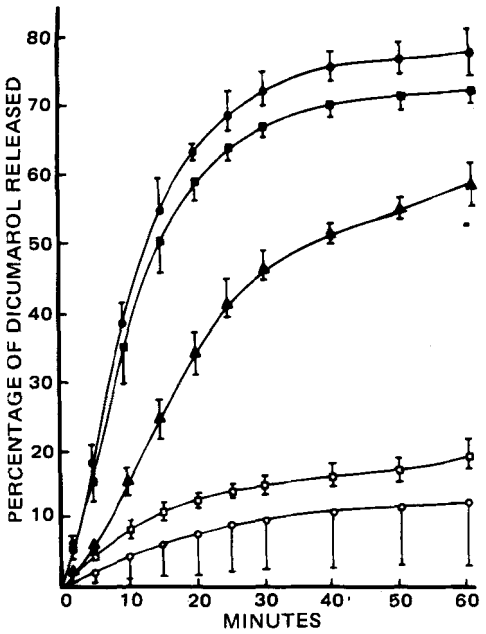

Figure 3—*Dissolution profiles of test tablets and a commercial product. Key: ●, 1:5 (w/w) dicumarol–polyethylene glycol 4000 dispersion; ■, 1:3 (w/w) dicumarol–polyethylene glycol 4000 dispersion; ▲, 1:1 (w/w) dicumarol–polyethylene glycol 4000 dispersion; ○, 1:5 (w/w) dicumarol–polyethylene glycol physical mixture; and □, commercial product.*

The inclusion of a lubricant, magnesium stearate, prevented tablet capping during direct compression. It was noted (18) that the incorporation of several magnesium compounds such as magnesium hydroxide and magnesium oxide into dicumarol formulations increased drug absorption. In that same study, magnesium stearate had no significant influence on the completeness of drug absorption, which is consistent with dissolution results in the present study showing equal or lower release rates for lubricant-containing tablets relative to those with no lubricant.

The apparent slower dissolution of dicumarol from the 1:1 dispersions compared to dispersions of higher percentages of polyethylene glycol 4000 could result from the greater portion of a slower dissolving diluent, lactose, in this formulation and/or to more extensive nucleation and conversion of a metastable to a less soluble stable form during the initial dissolution period. The latter explanation appears plausible considering the possible inhibitory effects of dissolved polymer on crystallization and recognizing that the low polymer to drug ratio tablet would supply the least polyethylene glycol concentration on dissolution. Substantial crystallization may occur initially if the levels of polymer in the bulk are below those necessary to inhibit renucleation. However, this explanation is probably inadequate since the 90-min percentages dissolved were not significantly different among the three ratios. In addition, predissolving the polymer did not alter the profiles for the 1:1 dispersion tablets. In experiments where the nondisintegrating tablets were removed from baskets after 20 min, 1:1 dispersion tablets appeared to dissolve slower. Thus, lactose dissolution may be rate limiting.

X-Ray Diffraction Studies—Spectra of unmilled dicumarol and milled polyethylene glycol 4000 appear in Fig. 4; spectra for the milled 1:1 dispersion and its physical mixture appear in Fig. 5. The major dicumarol diffraction peaks of 24.9, 26.9, and 11.8° could be identified in the solid dispersion sample as weak intensity peaks with ~18% of the intensity of drug alone in the physical mixture. All visible peaks for the physical mixture could be identified as those of polyethylene glycol 4000 or dicumarol. The intensities of major drug peaks were substantially greater in the physical mixture compared to the dispersion, which may indicate a loss in the drug's initial crystalline form during the fusion process. Peaks for the solid dispersions, appearing at ~23.4 and 20.8°, did not correspond to any of the major peaks noted for the polymer or drug. Other dicumarol peaks, such as measured at 10.4°, displayed increased intensity in the dispersion.

Observations of unidentifiable peaks accompanied by the disappearance of component peaks may be in accordance with spectral changes

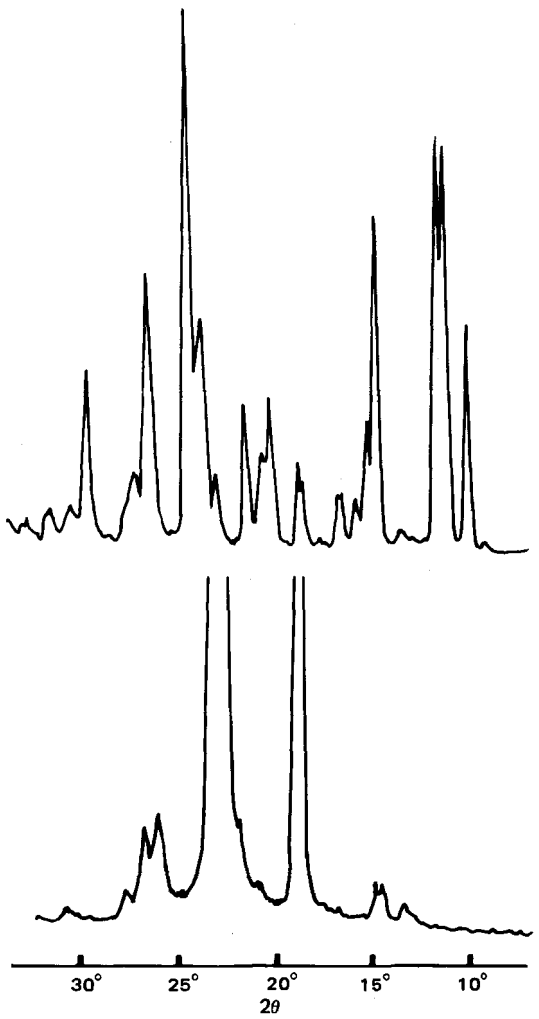

Figure 4—*X-ray diffraction spectra of dicumarol (top) and milled polyethylene glycol 4000 (bottom).*

expected for partial polymorphic conversion or solid solution. However, the presence of component peaks in the melts does not allow partial eutectic formation and particle-size reduction to be completely ruled out. The identification of well-defined peaks and the absence of a raising baseline seems to exclude amorphous drug formation as a major factor in the dispersion.

Dicumarol *In Situ* Absorption—*In situ* rat intestinal loops were utilized to examine dicumarol absorption from solutions prepared from drug alone, physical mixtures, and fusion dispersions. Solutions of high molecular weight polymer in the GI lumen may alter absorption by viscosity effects (31), solvent effects (32), and drug complexation (33). Table III shows the percentage of initial drug concentration remaining at 30 and 90 min for the recycling perfusion of jejunal segments. Dicumarol

Table III—Absorption of Dicumarol by Infused [a] *In Situ* Intestinal Loops

	Percentage Remaining to be Absorbed [b]			
Minute	Dicumarol Powder	1:5 Dicumarol–Polyethylene Glycol Physical Mixture	1:5 Dicumarol–Polyethylene Glycol Dispersion	Statistical Analysis [c]
0	100	100	100	
30	29.9 (4.9) [d]	36.1 (9.0)	34.7 (6.6)	NS [e]
90	22.4 (3.4)	22.7 (6.2)	29.9 (3.4)	NS [e]

[a] Recirculating infusion of a 15-cm segment at a rate of 4.8 ml/min. [b] Infusion buffer consisted of 60 ml of Krebs–Henseliet buffer with a dicumarol concentration of 10 μg/ml. [c] Analysis of variance with $p < 0.05$. [d] Mean ± *SD*; $n = 4$. [e] Not significant.

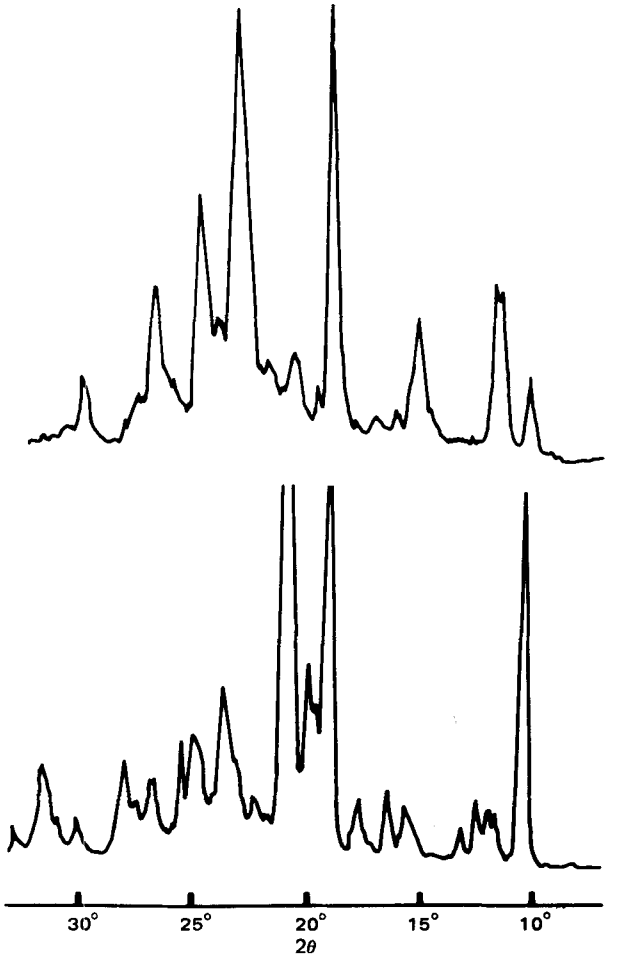

Figure 5—*X-ray diffraction spectra of 1:1 (w/w) dicumarol–polyethylene glycol 4000 physical mixture (top) and solid dispersion (bottom).*

rapidly disappeared from all perfusion buffers such that 68% was absorbed in the first 30 min. This initial rapid phase was possibly a result of tissue equilibrium since the absorption rates were substantially less during the 30–90-min interval. While initial *in situ* absorption was probably, in part, perfusion limited since the intestinal clearance rate of 2.3 ml/min was 48% of the perfusion rate, no significant effects of polyethylene glycol on this drug's absorption can be reported. These observations would confirm the absence of strong complexation as previously discussed as well as demonstrate that the polymer does not alter the membrane absorption of this drug *in situ*.

CONCLUSIONS

Observations of rapid drug disappearance from *in situ* loops and low equilibrium solubility would support previous statements (16, 19) of dicumarol's dissolution rate-limited character and, thereby, formulation sensitivity. The present study showed that the dissolution characteristics of dicumarol can be enhanced through the preparation of melt fusion products with polyethylene glycol 4000 without detectable degradation. Unlike other polyethylene glycol–drug (8) dispersion systems, complexation between drug and polymer cannot be considered as a factor contributing to higher dissolution rates for powders and tablets. Preliminary studies of X-ray diffraction patterns demonstrated that fusion products contained crystalline materials that could not be identified as either pure drug or polymer.

Further investigations employing differential thermal analysis and X-ray diffraction need to be performed to characterize the apparent high energy form of dicumarol in fusion dispersions. Based on X-ray microscopy and dissolution results, partial polymorphic conversion or solid solution formation seems to be an attractive explanation. After 1 year of storage for powders and direct compressed tablets, stability was unaltered and enhanced dissolution traits appeared unaffected. Investigations are currently being conducted with the aid of the described tablet dosage form to evaluate dicumarol's dissolution–bioavailability relationship.

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