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THE RELATIONSHIP BETWEEN THE PARTICLE SIZE OF DICUMAROL AND ITS BIOAVAILABILITY IN DOGS

PART II. DRUG SUBSTANCE

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ABSTRACT

Dicumarol crystals were milled to reduce their particle size. The milled and unmilled drug were each mixed with starch powder and the formulations were filled into capsules. A relationship was found between the particle size of dicumarol and its properties such as dissolution rate, inhibition of normal prothrombin activity and plasma concentration.

These data indicate that particle size, rather than crystalline nature, is the primary factor in determining the bioavailability of dicumarol from dry formulations.

INTRODUCTION

The present study was designed to investigate whether the particle size of the dicumarol (bis-hydroxycoumarin) crystals or the drugs crystalline nature is of primary importance in the bioavailability of the drug from dry formulations.

EXPERIMENTAL

Products Studied

The particle size of a lot of dicumarol crystals was determined by a single pass through a stack of sieves. A portion of the crystals was added to a ball mill and triturated for 6 hours with the aid of stainless steel balls. Superposition of the x-ray diffraction patterns of the ground and unground material indicated no change in crystalline nature due to the grinding process. The particle size analysis was repeated on the ground material. Table I shows the particle size profiles of the unmilled (U) and milled (M) drug.

Five grams of unmilled and milled dicumarol were each separately mixed with 17 g. of starch powder. The 22.7% dicumarol, starch powders were hand filled into number 3, hard gelatin capsules. The capsules were filled with the drug powder so

TABLE I

PARTICLE SIZE ANALYSIS OF DICUMAROL CRYSTALS

Sieve Number*	Percent Passed	
	Unmilled	Milled
80	99.5	98.0
100	99.0	97.5
120	96.0	96.0
140	90.0	94.0
170	83.0	91.0
200	70.0	89.0
270	63.0	87.0
325	42.0	85.0

*U.S.P. 1970, p. 940.

that each dog received 6 mg. of dicumarol per kilogram body weight.

The sixteen healthy female Beagle dogs had a weight range from 8.1 to 11.6 kg. and had no food administered after the capsule.

Particle size determination, dissolution, animal housing, protocol, prothrombin time measurements and assay for dicumarol were accomplished as described in Part I. Capsules.

Sixteen dogs were randomly assigned to either lot U (unmilled drug + starch) or lot M (milled drug + starch).

RESULTS AND DISCUSSION

Figure 1 shows photomicrographs of the capsule contents of the two lots studied. The contrast of the dark drug crystals with the colorless starch particles in the background is striking.

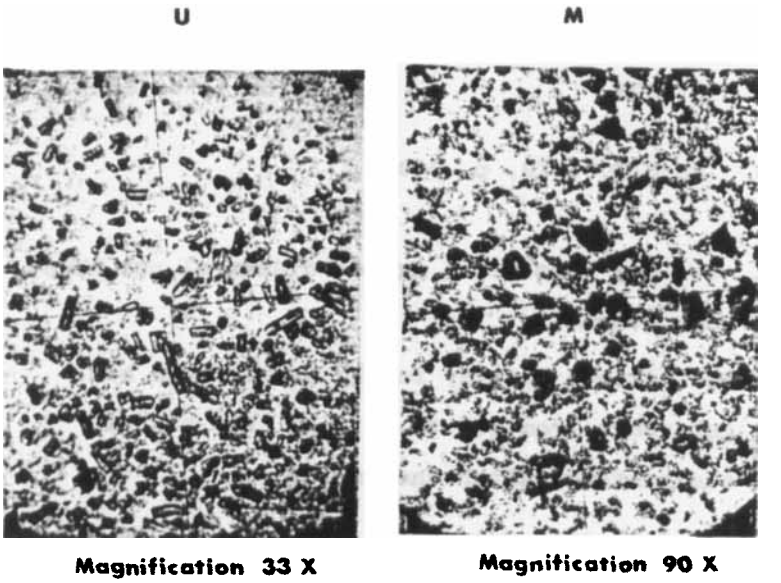

FIGURE 1. Photomicrographs of the contents of two different particle size dicumarol capsules.

The difference in the particle size of dicumarol from lot U capsules compared to that from lot M capsules is shown in Figure 2. The significant crystal size data are: lot U, 50% of the crystals are

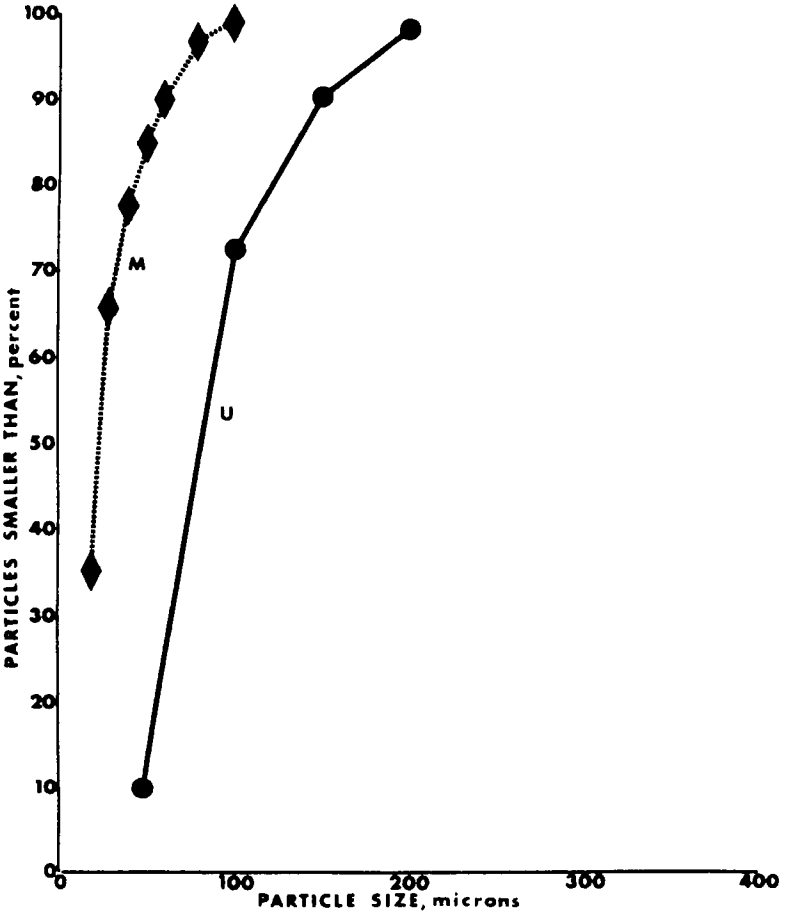

FIGURE 2. Particle size distribution of dicumarol crystals in two different capsules.

smaller than 85μ and 10% are smaller than 50μ. In lot M, 50% of the crystals are smaller than 25μ and 84% are smaller than 50μ.

The dissolution profiles of the two lots are graphically presented in Figure 3#. Dicumarol from each capsule of lot M dissolved more rapidly than that from any of the capsules in lot U.

Figure 4 depicts the mean percent inhibition of normal prothrombin activity after the administration of the two different lots of dicumarol capsules to the dogs. Capsules containing the milled drug produced the greater inhibition of normal prothrombin activity.

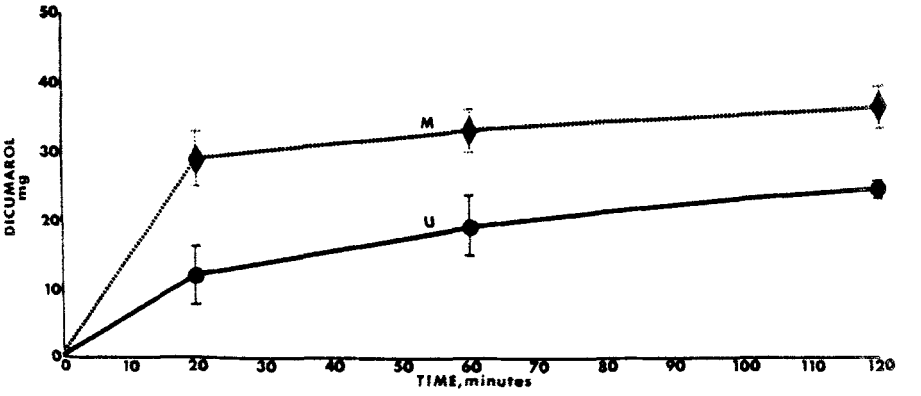

FIGURE 3. Mean dissolution of the dicumarol from two different particle size dicumarol capsules.

The bars represent one standard deviation.

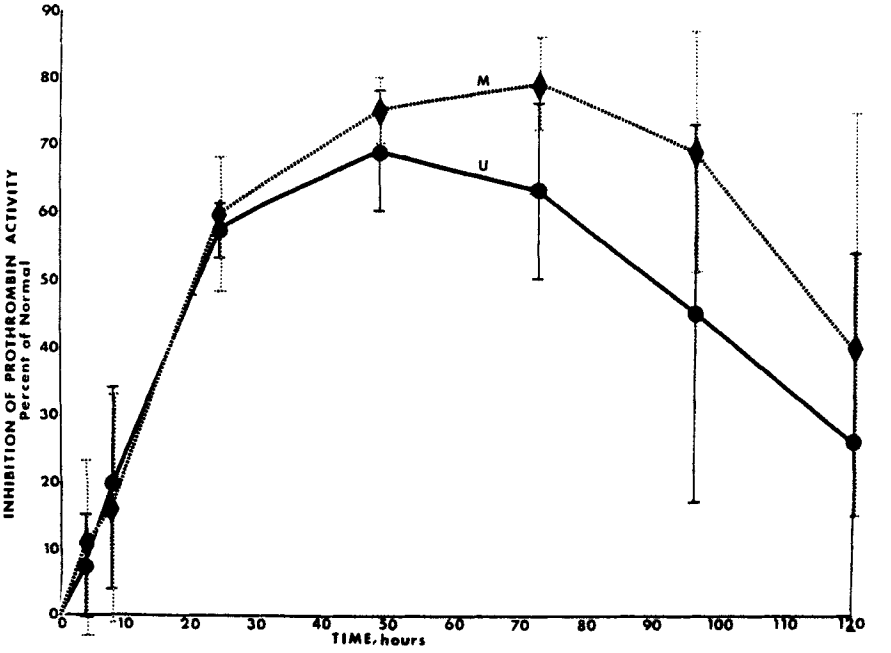

FIGURE 4. Mean percent inhibition of normal prothrombin activity in dogs after administration of two different particle size dicumarol capsules.

The mean plasma concentration-time curves are shown in Figure 5. Lot M, containing the smaller particle size drug, is associated with earlier and higher plasma concentrations as well as greater area under the curve.

The log-linear relationship between the plasma concentration of dicumarol and the prothrombin complex activity synthesis rate is pictured in Figure 6. Higher plasma concentrations cause greater inhibition of prothrombin complex activity synthesis rate.

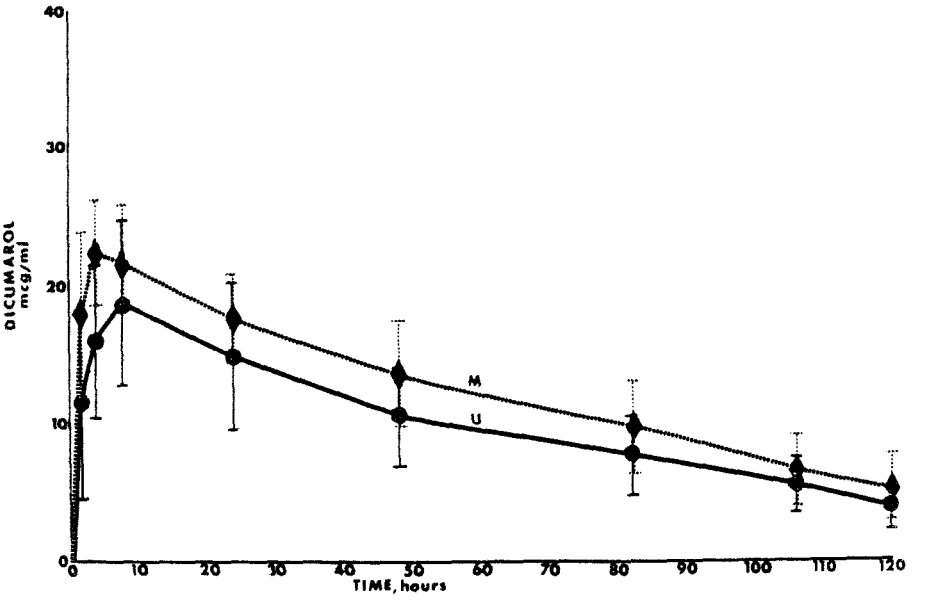

FIGURE 5. Mean plasma concentrations of dicumarol in dogs after administration of two different particle size capsules.

Figure 7 is a plot of the area under the percent inhibition of normal prothrombin activity (PINPA)-time curve and the area under the plasma concentration-time curve against the amount of dicumarol in solution after 120 minutes. Although considerable variability exists within each lot, rank order correlation was indicated. (See Part I. Capsules.)

In Figure 8, the relationship between the area under the PINPA-time curve and the area under the plasma concentration-time curve for lots U and M

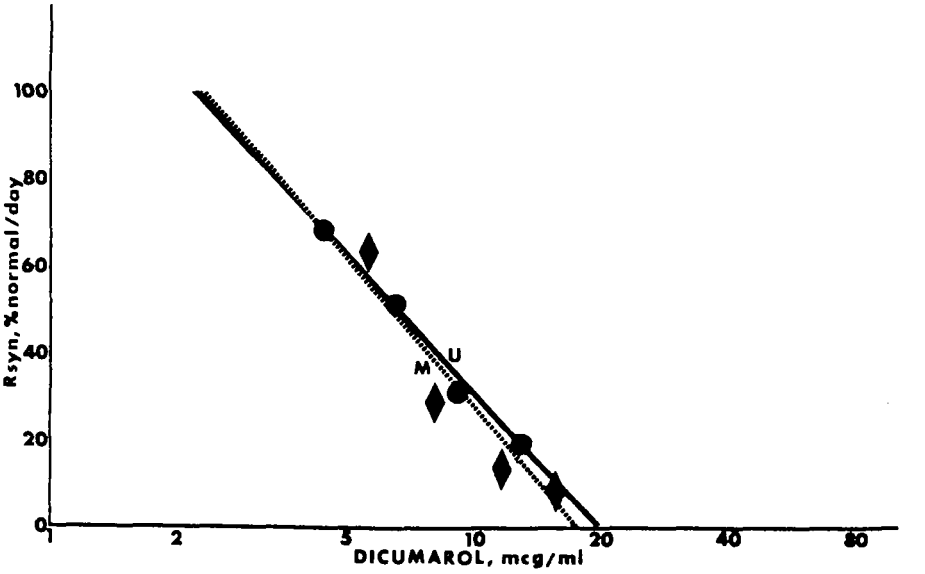

FIGURE 6. Relationship between synthesis rate of prothrombin complex activity and plasma dicumarol concentration after administration of two different particle size dicumarol capsules.

is indicated. A rank order is obtained which is inconsistent within each lot. However, the greater PINPA-time area is associated with greater plasma dicumarol-time area.

SUMMARY

A bioavailability study in dogs of dicumarol crystals, prepared from the same lot of drug substance, but milled to different particle size was completed. A relationship between the particle size of dicumarol and the following characteristics

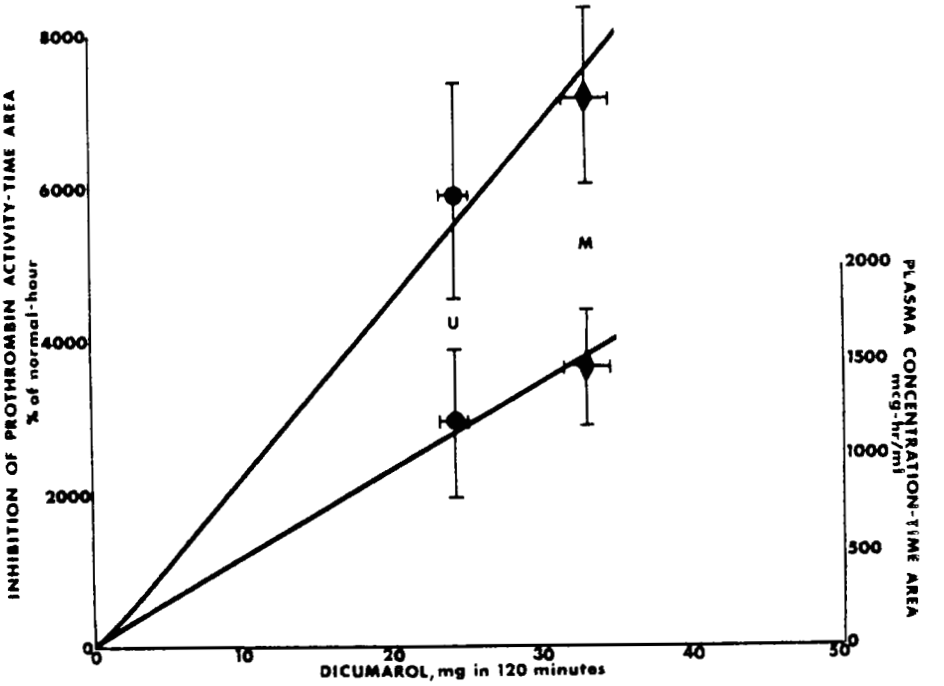

FIGURE 7. Correlation between dissolution of dicumarol and area under plasma concentration-time curve or area under percent inhibition of normal prothrombin activity-time curve.

has been shown; dissolution rate, plasma concentration and percent inhibition of normal prothrombin activity of the drug. Smaller particles of dicumarol are associated with a more rapid dissolution rate, a greater PINPA, and a higher plasma concentration of the drug.

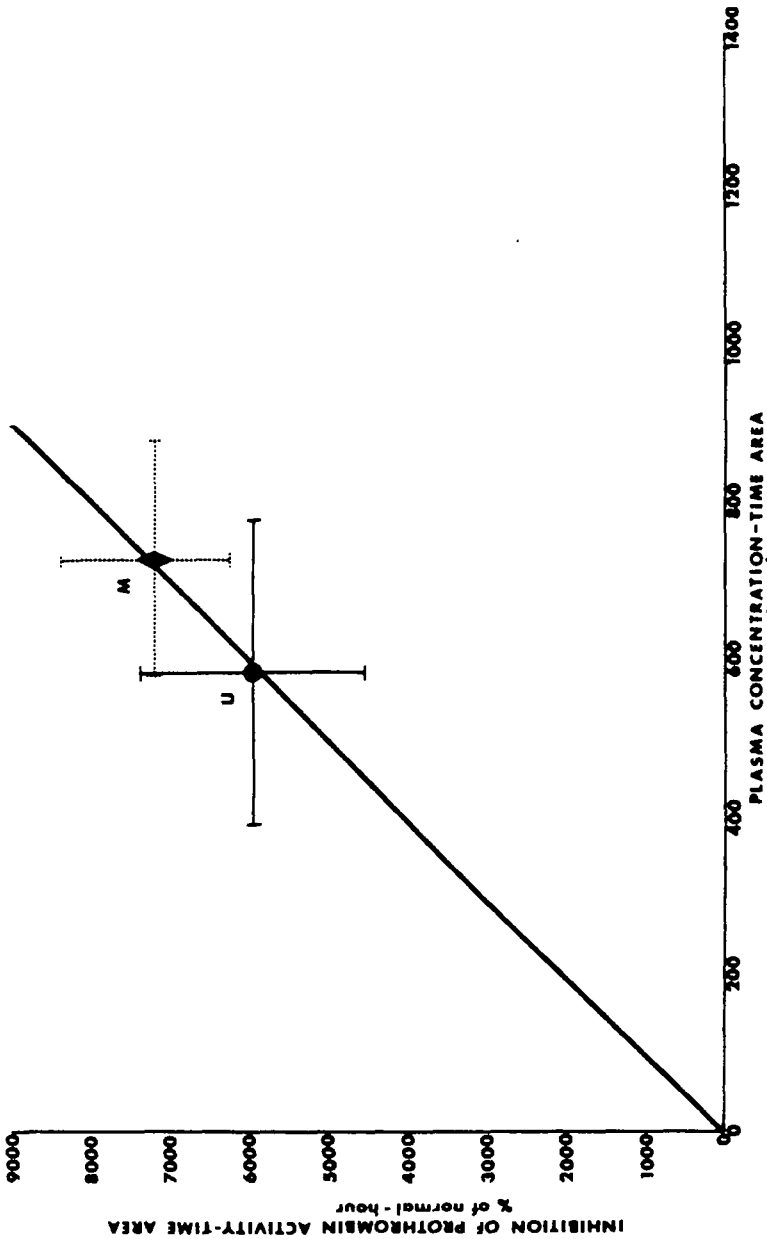

FIGURE 8. Relationship of percent inhibition of normal prothrombin activity-time area to the plasma concentration-time area of two different particle size dicumarol capsules.

A linear relationship was found between the prothrombin complex activity synthesis rate and the logarithm of the dicumarol plasma concentration. The dissolution of the two lots studied correlates with the areas under the plasma concentration-time curves and the areas under the percent inhibition of normal prothrombin activity-time curves. Also, areas under the plasma concentration-time curves correlate with the areas under the PINPA-time curves.

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