Interaction between DNA and Coralyne Acetosulfate, an Antileukemic Compound

Keyphrases ☐ Coralyne acetosulfate—interaction (complexation) with calf thymus DNA in water ☐ DNA (calf thymus)—interaction (complexation) with coralyne acetosulfate in water

Sir:

The alkaloid coralyne displayed confirmed antileukemic activity against leukemias L-1210 and P-388 in laboratory animals. A practical preparation of the acetosulfate (sulfoacetate) and the chloride salts of coralyne was recently reported (1); the availability of this method has permitted an easy access to this alkaloid, thus permitting unhampered the continuation of biological, pharmacological, and clinical evaluation. Although the exact mode of action of coralyne is not yet understood, a comparative study of UV absorption characteristics revealed an *in vitro* interaction between coralyne and calf thymus DNA in aqueous solution. This phenomenon may be associated with the biological activity of coralyne.

When coralyne acetosulfate (I*a*) was dissolved in water, the UV absorption of the aqueous solution at pH 7 changed rapidly. The major absorption peak of the solution moved from 297 to 262 nm. within 1 hr. This hypsochromic shift was practically complete after 2 days (Fig. 1; the same phenomenon was observed with the less water-soluble chloride salt I*b*). However, when a 1:4 (weight ratio) mixture of I*a* and the sodium salt of calf thymus DNA[1] was dissolved in water at pH 7, the UV spectrum of this complex, which is different from that of either component under the same controlled conditions, showed no change on standing. Even after the solution was allowed to stand at 25° for 4 weeks, the shape of the UV spectrum remained practically unchanged (Fig. 2). Under similar conditions, when the thymus DNA was dissolved in water at pH 7, the UV spectrum showed a single peak at 258 nm. (Fig. 1) which slowly decreased in peak height on standing. A

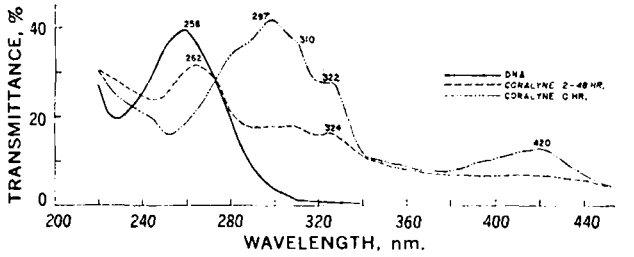
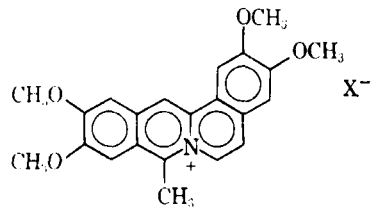


Figure 1—*UV absorption of coralyne and DNA in water at pH 7, 25° [coralyne acetosulfate, 5 mg./l.; and DNA (calf thymus, sodium salt), 20 mg./l.].*

[1] Calbiochem.



I*a*: X = $CH_3CO_2SO_3^-$
I*b*: X = Cl

precipitate formed after the aqueous DNA solution was stored at 25° for 4 weeks.

Coralyne acetosulfate apparently undergoes a rapid hydration process in aqueous solution. Presumably this is due to multiple bond hydration (2–4) across the C=N region, which results in breaking of the original conjugative system and, hence, alters the electronic transitions. The hydration is reversible; when an aqueous solution containing I*a* was kept at 25° for 2 hr. followed by subsequent lyophilization, the resulting solid showed an identical melting point and IR and UV spectra in methanol (Fig. 3) as the original material, I*a*. Under similar conditions, methanol was not added across the C=N bond, since the UV absorption peak remained unchanged even after long standing.

These results revealed that an interaction between coralyne and thymus DNA in water existed and that the resulting complex blocked the breaking of aromatic conjugation of coralyne by covalent hydration. These observations are significant since complex formation between many biologically active compounds with DNA double helix has been suggested to account for their activity (5–13). Also, a common N—O—O— triangulation feature, which was found among a number of antileukemic compounds including coralyne, has been proposed as a possible pharmacophore, which may contribute to the *in vivo* binding to some biologically pertinent sites (14). Detailed studies on hydration of coralyne as well as certain related problems are being actively performed.

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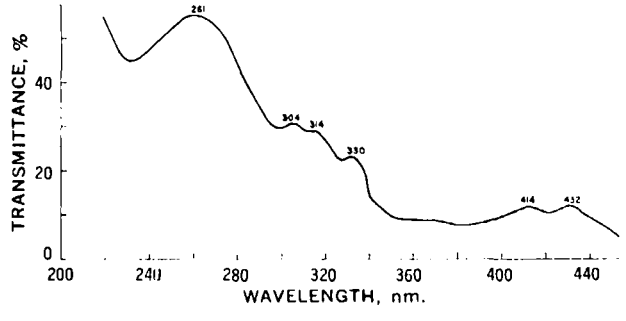

Figure 2—*UV absorption of DNA–coralyne in water at pH 7, 25° [coralyne acetosulfate, 5 mg./l.; and DNA (calf thymus, sodium salt), 20 mg./l.].*

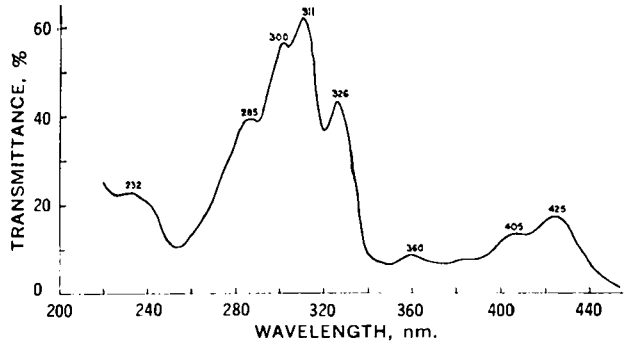

Figure 3—*UV spectrum of coralyne (acetosulfate) in methanol (5 mg./l.).*

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Effect of Formulation on Dissolution of Sodium Warfarin Tablets

Keyphrases □ Sodium warfarin tablets—effect of pregranulation dissolving on dissolution rate □ Dissolution rate, sodium warfarin tablets—effect of dissolving drug prior to granulation

Sir:

Numerous publications have shown that formulation of a solid dosage form can influence dissolution of the active drug. These studies have discussed the effect of binder concentration and tablet hardness (1), types of binders and particle size (2), types of starches (3), lubricants (4), and disintegration agents (5).

Table I—Dissolution Rate Constants (k) of Various Sodium Warfarin Tablet Formulations and Surface Tension of Solutions Used to Granulate

Formulation	k, min.$^{-1}$	Surface Tension[a], γ, dynes/cm.
A. Drug incorporated in dry form	0.060	—
B. Drug and polyvinylpyrrolidone dissolved in alcohol[b]	0.074	26.1
C. Drug dissolved in alcohol[c]	0.113	25.6
D. Drug and polyvinylpyrrolidone dissolved in water[d]	0.154	57.4
E. Drug dissolved in water[e]	0.246	59.4
	Absolute alcohol	24.4
	Water, deionized	74.1

[a] Of solution used to granulate. Measured by a Du Noüy interfacial tensiometer. [b] Solution ratio of drug–polyvinylpyrrolidone–alcohol = 1:1:6. [c] Solution ratio of drug–alcohol = 1:6. [d] Solution ratio of drug–polyvinylpyrrolidone–water = 1:1:4. [e] Solution ratio of drug–water = 1:4.

The purpose of this communication is to report that dissolving sodium warfarin prior to granulating can influence the dissolution rate.

Sodium warfarin was incorporated into a microcrystalline cellulose–lactose (3:1) mixture such that 25 mg. of sodium warfarin was contained/275-mg. tablet. The drug was either added into the formulation in the dry state or dissolved in an aqueous or alcoholic media, with or without an equal ratio of polyvinylpyrrolidone–sodium warfarin. The solutions (Table I) were used to granulate the microcrystalline cellulose–lactose mixture. Magnesium stearate (0.1%) was added to either the powder mixture or the dried, 20-mesh screened granulation. Tablets were compressed on a compressing machine[1]. All tablets disintegrated within 1 min. Dissolution tests were performed in a round-bottom flask, containing 500 ml. of distilled water, maintained at 37°. A half-moon (2.5 cm. in diameter) stirring blade was used at a speed of 50 r.p.m. Assays were performed spectrophotometrically.

The pseudo-first-order rate constants obtained from this study are shown in Table I. As can be seen, the slowest rates are obtained when the drug is in the dry state or is dissolved in an alcoholic polyvinylpyrrolidone solution. Dissolution can be increased when the drug is dissolved in water—with or without polyvinylpyrrolidone—or in alcohol alone prior to granulating.

By dissolving the drug prior to granulating, it is possible to increase the available surface area when this solution is poured onto a powder mixture. This would result in increased dissolution (Table I).

The difference in the rate of solution between Formulations C and E appears to be a function of the surface tension of the solution used to pour onto the lactose–microcrystalline cellulose mixture. It is known that the high surface area of microcrystalline cellulose is due to fissures and crevices found abundantly in the granules. Since the alcoholic solution (Formulation C) has a

[1] Colton SX, four station.