HYDRODYNAMIC RADII OF PHENOTHIAZINE MICELLES : A LASER LIGHT SCATTERING STUDY

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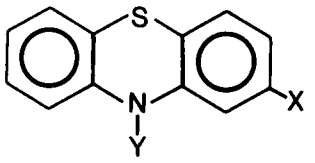
Investigations into the aggregation of phenothiazines using various techniques have been documented (Attwood 1974; Florence 1971). Such surface activity studies may be important in many fields, including the stability of solutions, the monitoring of interactions during pharmaceutical formulation, and in bioavailability assessments.

We used photon correlation spectroscopy to examine a series of phenothiazines (Fig. 1) at various concentrations in 0.15M NaCl at 25 ± 0.1°C and at approximately pH 5 (well below their pK_a's). This is the first time the technique has been used in such a way for these drugs. Diffusion coefficients were derived from linear least square fits and the appropriate hydrodynamic radii ($\bar{R}_h$) were calculated via the Stokes-Einstein equation.

Fig.1



	X	Y
△Promethazine	H	CH_2-CH.N(CH_3)$_2$.HCl (CH$_3$ branch)
○Promazine	H	$(CH_2)_3N(CH_3)_2$.HCl
■Chlorpromazine	Cl	$(CH_2)_3N(CH_3)_2$.HCl
▲Triflupromazine	CF_3	$(CH_2)_3N(CH_3)_2$.HCl
●Thioridazine	SCH_3	$(CH_2)_2$-piperidine(N-CH_3).HCl

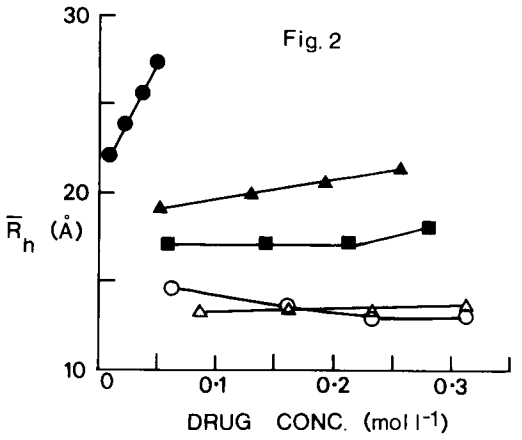


Fig. 2

The results illustrated in Fig. 2 (S.D. < 1%, n = 10) indicated that for any particular drug concentration, the hydrodynamic radius of the micellar aggregate depended on the phenothiazine structure. The more hydrophobic drugs formed larger micelles so that the size increased in the order promethazine, promazine, chlorpromazine, triflupromazine and thioridazine. Zografi and Munshi (1970) similarly reported a correlation between surface activity and the hydrophobicity of such molecules. The branching of the alkyl group at position Y slightly reduced the surface activity and the hydrodynamic radius of promethazine, at low concentrations, compared with promazine; a Cl or CF_3 group at position X increased the micellar size. Thioridazine, which provided the highest radii, has a -SCH_3 group at X and a piperidine ring on the alkyl side chain at Y, which greatly enhanced the hydrophobicity of this chain. Substitution of the phenothiazine nucleus also affected the way in which the hydrodynamic radius altered with increasing drug concentration. The more hydrophobic was the drug, the more marked was the increase in micellar size with change in concentration.

Attwood, D. et al (1974) J. Pharm. Sci. 63: 988-993
Florence, A.T., Parfitt, R.T. (1971) J. Phys. Chem. 23: 3554-3560
Zografi, G., Munshi, M.V. (1970) J. Pharm. Sci. 59: 819-822

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