Water as a Nonpolar Partition Medium

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Abstract □ Coacervates have been suggested as models for cytoplasm since cytoplasm is also essentially an aqueous phase of water–protein–colloid complexes. This study on partition coefficient properties made use of coacervate phases as the nonpolar phases in equilibrium with polar water phases. The partition coefficients of four barbiturates were obtained, and their values correlated with those reported in the literature for systems using organic solvents as the nonpolar medium. These values also correlated with reported values for the absorption ranking of the barbiturates in the rat colon. The partition coefficients of theobromine and theophylline in gelatin–benzalkonium chloride coacervate systems were also found to correlate with the partition values reported in the literature for heptane–water and chloroform–water systems. It is suggested that coacervate systems form a more realistic model for studying and predicting the absorption characteristics of drugs than do conventional organic solvent–water systems.

Keyphrases □ Partition coefficients—various barbiturates and xanthines, coacervates as nonpolar phases in equilibrium with polar water phases □ Barbiturates, various—partition coefficients, coacervates as nonpolar phases in equilibrium with polar water phases □ Xanthines, various—partition coefficients, coacervates as nonpolar phases in equilibrium with polar water phases □ Coacervates—nonpolar phases in equilibrium with polar water phases, partition coefficients, various barbiturates and xanthines

Meyer (1) and Overton (2) showed a correlation between anesthetic drug activity and the partition coefficient, *i.e.*, the ratio of drug solubility in a lipoid phase to its solubility in a water phase. For the lipoid phase, olive oil, corn oil, chloroform, and a spectrum of nonpolar organic solvents have been used. Water can act as a nonpolar solvent when it is bound to various molecules (proteins, surface-active agents, *etc.*) to form a liquid that is insoluble in a regular or bulk liquid water. This nonpolar structured water complex is referred to as a coacervate. Coacervates have been suggested as models for cytoplasm since cytoplasm is also essentially an aqueous phase of water–protein–colloid complexes (3, 4).

This report considers the use of a coacervate system as the nonpolar phase in equilibrium with a normal water phase.

BACKGROUND

The partition coefficients of four barbiturates were obtained, and the values were compared to those reported in the literature using an organic nonpolar medium (5). Schanker (5) studied the absorption of barbiturates from the rat colon and compared the percent absorption with the partition coefficients of the free acids in chloroform–water systems. The reported percent absorption values are compared here with the partition coefficient values of the barbiturate salts in a coacervate–water system.

The partition coefficients of theobromine and theophylline in gelatin–benzalkonium chloride coacervate systems were obtained and compared to those reported for heptane–water and chloroform–water systems (6). Comparisons were also made to percent drug absorption in the rat colon as reported in the literature (6).

The rationale for attempting to correlate partition coefficients of compounds with reported values for percent absorption is as follows. Since coacervates, regardless of their composition and pH, are complex aqueous colloidal systems, it is expected that they bear more resemblance in overall properties to protoplasm than do lipids and lipid-like solvents such as chloroform and heptane. Any correlation between interactions of compounds with coacervates, as evidenced by preferential uptake or exclusion, and absorption profiles of these compounds can be considered to support the hypothesis that complex coacervates systems (not necessarily the systems considered in this work) can be considered as models for protoplasm. It is obvious that barbiturates are not appreciably ionized at physiological pH. However, since the properties and interactions of the salts reflect, in some ways, the properties of the parent compounds, it is not unreasonable to attempt correlation of salt–coacervate interactions with absorption characteristics.

EXPERIMENTAL

Preparations of Coacervate System—In 15-ml graduated tubes, 3.0 ml of a 10% gelatin solution, 2.0 ml of a 5% benzalkonium chloride solution, and sufficient 0.1 *N* sodium hydroxide were added to give a pH above 9. This solution was diluted to 15 ml with distilled water. The tubes were stoppered, mixed vigorously, and left undisturbed for 24 hr at 37°. Complete separation of two aqueous phases occurred. The bottom layer was the coacervate and contained most of the colloidal material.

Assay of Drug by Difference—The concentration of the barbiturates used in this study was determined spectrophotometrically. The concentration of the compound in the coacervate was determined from the difference between the total amount in the system and the amount spectrophotometrically found in the equilibrium liquid. The sodium salts of barbital, phenobarbital, pentobarbital, and secobarbital were studied at 37°. The concentration of the salts in equilibrium liquid was determined at 240 nm, using a 0.2 *M* borate buffer (pH 9.6) as the diluting solvent and a total system concentration of 200 mg %.

Partitioning of theophylline and theobromine was studied at 37°. Theophylline dilutions were prepared in a potassium chloride–sodium hydroxide buffer of pH 12 and measured at 275 nm. The same solvent was used for theobromine, which was measured at 274 nm. The partition coefficients (P.C.) were obtained at 50 and 100 mg %, and the average values are reported in Table I.

RESULTS AND DISCUSSION

The partitioning patterns of barbiturate salts are shown in Fig. 1. Barbital sodium showed the least uptake in coacervates. At concentrations higher than 100 mg %, it exerted a suppressive action on coacervation as evidenced by a decrease in the volume of the coacervate layer. At a concentration of 200 mg %, the compound was distributed equally between the two phases.

Barbital sodium did not show a precipitation–resolubilization interaction with benzalkonium chloride, which explains its weak affinity for coacervates. The partitioning isotherms for the sodium salts of phenobarbital, pentobarbital, and secobarbital showed a strong affinity of these salts toward coacervates and the dependence of this affinity on the concentration of the salt.

Schanker (5) studied the absorption of barbiturates from the rat colon and compared the percent absorption with the partition coefficient of the free acids in chloroform–water systems. Figure 2 shows the correlation between the percent absorption and the partition coefficient of the barbiturate salts in gelatin–benzalkonium chloride systems. The averages of the partition coefficients at the four highest concentrations studied

Table I—Partition Coefficient Studies of Theophylline and Theobromine[a]

Compound	Percent Absorbed	Partition Coefficients: Heptane–Water	Chloroform–Water	Coacervates
Theophylline	30	0.02	0.3	3.32
Theobromine	22	0.002	0.4	2.37

[a] The data, with the exception of the partition coefficients in coacervates, are from Ref. 6.

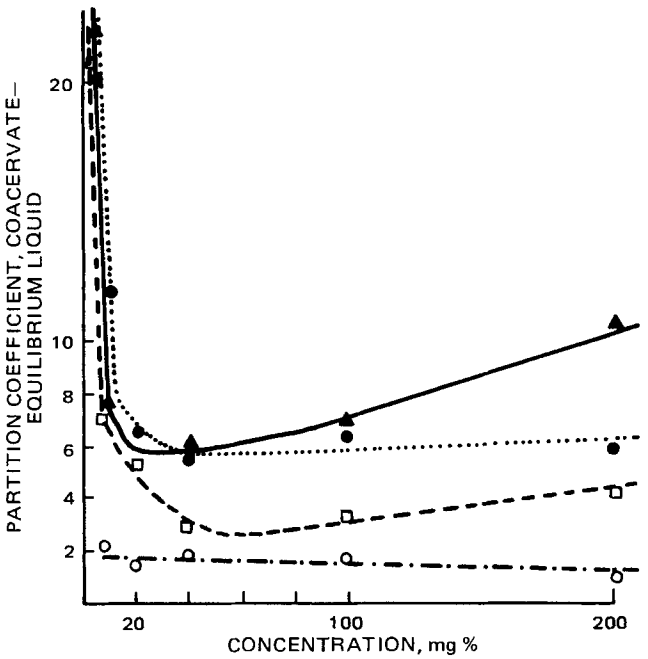

Figure 1—*Partitioning of barbiturate salts in gelatin–benzalkonium chloride system at 37°. Key: ▲—▲, secobarbital sodium; ●·····●, pentobarbital sodium; □- - -□, phenobarbital sodium; and O----O, barbital sodium.*

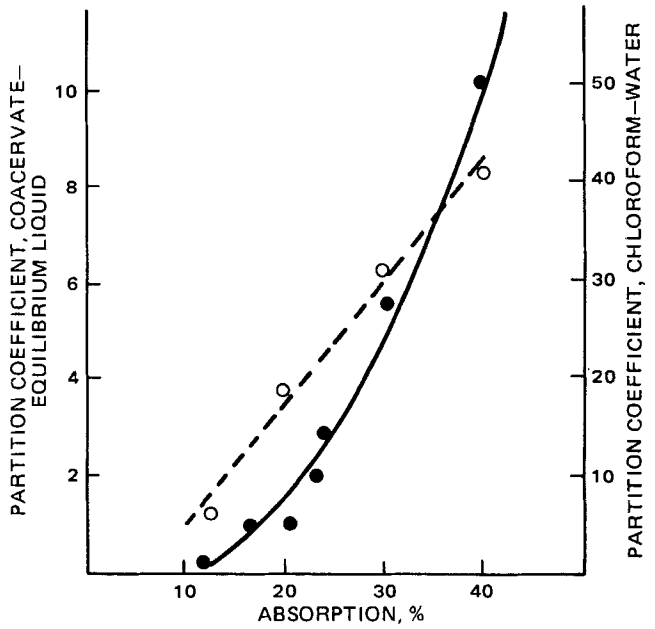

Figure 2—*Correlation of the partition coefficients of barbiturate salts with percent absorption from the rat colon. Data for percent absorption and chloroform–water partition coefficients are from Schanker (5). Key: O- - -O, partition coefficient, coacervate–equilibrium liquid, of barbiturate salts; and ●—●, partition coefficient, chloroform–water, of free acids.*

(20–200 mg %) were plotted *versus* the percent absorption as reported by Schanker. The choice of these average values was arbitrary and based on the assumption that the average partition coefficient over a wide concentration range was more representative of the intrinsic affinity between the coacervate and the barbiturate salt and tended to cancel the effects of any secondary interactions between the compound and the components of the coacervate.

Table I shows the intestinal absorption of theobromine and theophylline in relation to their partition coefficients in heptane–water, chloroform–water, and gelatin–benzalkonium chloride systems. It is obvious that there exists a better correlation between the percent absorption and the partitioning in coacervates than between the absorption and the partitioning in nonpolar organic solvents.

These coacervates are particularly useful for studying partitioning of water-soluble salts of insoluble weak acids between coacervates and their equilibrium liquids. The hypothesis underlying these studies is that the differences between the "hydrophobicity" of these anions will be manifested in their affinity (*i.e.*, partitioning) for structured water in the coacervate phase.

There is a clear correlation between variables in the experiments using barbiturates and xanthines, suggesting that coacervates of this type might serve as biological models for studying and predicting the absorption characteristics of drugs.

The purpose of benzalkonium chloride is to act as a coacervating agent in the system. The gelatin used has an isoelectric point of 8.2. Above this pH, gelatin is negatively charged and, under the proper conditions, forms true complex coacervates with benzalkonium chloride. Most of the studies on coacervation of gelatin with, for example, acacia involved gelatin of a lower isoelectric point and the pH of coacervates was, generally, on the acid side. At the time of these studies, true complex coacervation between a high isoelectric point gelatin and other ingredients, particularly surface-active agents, had not been reported in the literature.

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