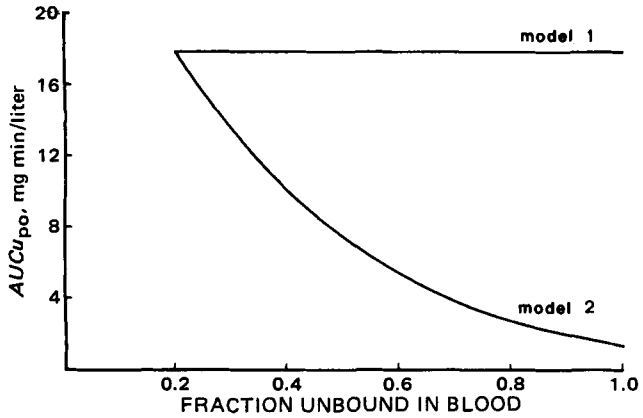

Figure 2—*Effect of fraction of unbound drug in blood on* AUC *of unbound drug concentration (*$AUCu_{po}$*) versus time for 200 mg of meperidine administered orally.*

the isolated perfused rat liver preparation. It is theoretically possible to vary the fraction of unbound drug in the perfusate by at least 10-fold for a highly bound drug, whereas the hepatic perfusion rate may only reasonably be varied by less than twofold (3). A preliminary investigation of the plasma protein binding of propranolol has been carried out using equilibrium dialysis. The results of this investigation show that it is possible to achieve a 10-fold variation of the fraction of unbound drug by varying the concentration of bovine serum albumin and α_1-acidglycoprotein in the perfusate[1].

The predictions of models 1 and 2 for the relationship between free fraction in blood and the steady-state unbound drug concentration in the reservoir of the isolated perfused rat liver preparation (Cu_{ss}) following constant-rate drug administration into the portal vein are analogous to those described for $AUCu_{po}$. The equations relating fraction of unbound drug in blood with Cu_{ss} can be derived from the equations presented by Pang and Rowland (7) and for model 1:

$$Cu_{ss} = \frac{R}{CLu_{int}} \qquad \text{(Eq. 5)}$$

and for model 2:

$$Cu_{ss} = \frac{fu_b\, Re^{(-fu_b\, CLu_{int}/Q_H)}}{Q_H[1 - e^{(-fu_b\, CLu_{int}/Q_H)}]} \qquad \text{(Eq. 6)}$$

where R is the infusion rate of drug into the portal vein.

Hence, the effect of changing free fraction of drug in perfusate on the steady-state unbound drug concentration in the reservoir following constant-rate drug administration into the portal vein in the isolated perfused rat liver preparation may also be used to discriminate between the two models.

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Filter-Probe Extractor: A Tool for the Rapid Determination of Oil–Water Partition Coefficients

Keyphrases □ Filter-probe extractor—tool for rapid determination of oil–water partition coefficients □ Oil–water partition coefficients—rapid determination using filter-probe extractor □ Thermodynamics—filter-probe extractor use for rapid determination of oil–water partition coefficients

To the Editor:

The distribution of solutes between water and oil has been the subject of hundreds of studies since the end of the last century (1). The oil–water partition coefficient [or liquid–liquid distribution constant, as recommended (2) by IUPAC] is of use in separation science as it indicates the extent of extraction in a two-phase system. Also, since the partition coefficient is taken (3) as a measure of solute hydrophobicity, it is an often used parameter in, for example, preformulation and drug design (QSAR) studies. Partition coefficients have been determined by a large number of methods, including shake flask, counter-current distribution (4), and various automated methods including the AKUFVE (5) and SEGSPLIT (6) approaches.

Recently, we published a study (7) on the thermodynamics of solute oil–water partitioning, where use was made of a modification of a rapid solvent extraction method described by Cantwell and Mohammed (8) for photometric acid-base titrations in the presence of an immiscible solvent. Using various data manipulations, these workers have been able to demonstrate (9, 10) that their method provides ion-pair distribution coefficients and is of consequent use in drug analysis. Here we wish to communicate some of our experiences with a modified filter-probe for measuring oil–water partition coefficients of molecules of pharmaceutical interest, and to draw attention to the fact that the method has particular use for the examination of the effect of a large number of variables on the distribution process. It is emphasized that the apparatus here described is similar to, but not the same as, that developed by Cantwell and Mohammed.

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The apparatus consists of an efficient mixing chamber (fitted with vortex spoilers and a well-sealed lid), one or two filter probes immersed in the mixed phases, and a pumping system that pumps the probed phase(s) through a spectrophotometric flow-through cell and back to the mixing chamber (see refs. 7 and 8 for schematics). The mixing chamber is thermostated and can have a volume from 50 to 1000 ml. Figure 1 gives the design of our modified filter probe, which is machined out of a stainless steel block. There is almost zero contact between the phases and the protective polytef spacer, compared to the polytef mesh (8) and wafer (10) that Cantwell and Mohammed place behind their filter material (to increase flow).

With our earlier experiments on the partitioning of hydrophobic drugs, it was found that using the latter configurations adsorption of drug onto the polytef was a problem. With the modified probe, postfiltration flow is improved by 20 radial channels (0.2-mm depth) cut into the surface of the cylindrical stainless steel block. Adsorption to polytef was such an early problem that all connecting tubing is now constructed of an HPLC-grade 1.0-mm bore stainless steel tube. In addition, HPLC pumps are used to effect flow, since these give no adsorption problems (unlike peristaltic pumps) and can be readily used with volatile solvents.

For our studies, a cellulose filter paper[1] was used for the probing of the aqueous phase and a polytef film[2] for probing of the oil. (Any hard cellulose filter paper should suffice for the hydrophilic filter probe.) We prefer to monitor the aqueous phase, and as a general procedure add only aqueous phase to the system, pump, adjust recorder baseline, add solute in a volume of the aqueous phase; after further equilibration (given by constant recorder reading), add a volume of oil, equilibrate, add an equal volume of oil, equilibrate, add a third equal volume of oil, and equilibrate. Since it takes between 0.5 and 15 min to reach equilibration (depending on pumping rates, phase volumes, and partition coefficient), one can very quickly determine from these experiments the effect of solute concentration on distribution. One can then go on to study the effect of various variables on the partitioning process; *e.g.*, temperature can be altered if the thermodynamics are to be studied, or a pH stat can be employed to obtain the pH–partition profile of a compound and hence determine the pKa.

Since the method is rapid, it can be used to determine the partition characteristics of relatively unstable compounds. Phase volume ratios of 1000:1 are possible, though the probed phase must have a volume greater than that of the pumping circuit. The range of partition coefficients that can be measured is $\sim +5.3$ to -5.3 log units, though this is dependent on the sensitivity of the analytical method. Generally, a pumping rate of between 1.0 and 1.5 ml/min is used: greater speeds result in overloading of the filter system.

There are three potential disadvantages to the procedure: One is evaporation of solute. This was found for benzene in our original experiments, and has since been described[3] as a problem common to all conventional methods for determining the partition coefficient of benzene, but which should be circumvented by the use of a closed system. The second, more serious problem, is that of adsorption. This has been circumvented in our system by employing stainless steel fittings and tubing and HPLC pumps, but it could still be a problem for some very polar compounds. Adsorption is very clearly seen in the step before addition of oil by a continuing fall in recorder reading, which is seen to be reversible during washing. Another problem encountered is the use of silicon-based filters as hydrophobic probes when cyclohexane and 2,2,4-trimethylpentane are used. Here it is found that after a short time the filters become permeable to the aqueous phase, due to a stripping of the filter material.

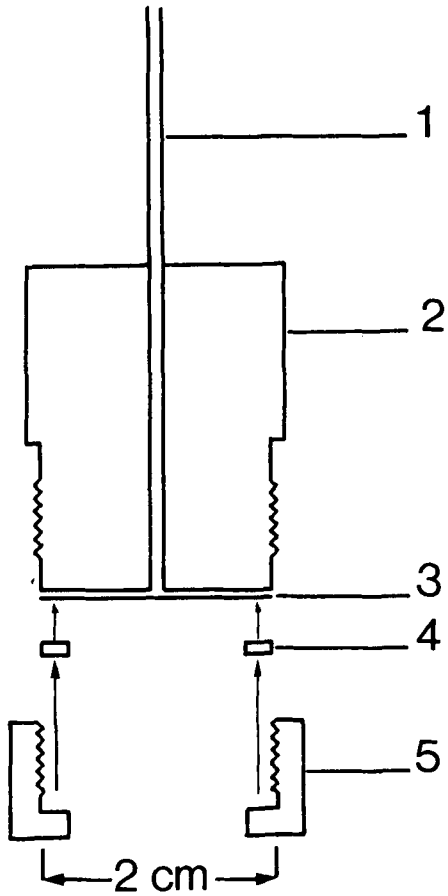

Figure 1—*Filter-probe extractor. 1, 1.0-mm bore stainless steel tube; 2, cylindrical stainless steel block; 3, filter material; 4, polytef o-ring spacer; and 5, screw-on stainless steel cap.*

To date, this modified filter probe system has been used in our laboratory for a number of studies including the aforementioned thermodynamics study and the determination of the partitioning of unstable compounds, peptides, and various hydrophilic and hydrophobic neutral drugs. Cyclohexane, 2,2,4-trimethylpentane, 1-octanol, and chloroform have all been successfully employed as oil phases. Table I illustrates the close agreement between partition coefficients determined by both conventional shakeflask and the described filter-probe methods (7). The filter probe system can be described as a simple and convenient tool for not only determining ion-pair equilibria (8–10), but also, as discussed here, both for "one-off" determination of solute oil–water partition coefficients, and

[1] 589/3 Blauband filter paper, Schleicher and Schüll
[2] Mitex LC 10-μm with 68% porosity, Millipore.
[3] C. Hansch, Pomona College, Calif., personal communication.

Table I—Comparison between Shake-Flask and Filter Probe Methods for Determining Partition Coefficients between Oil [a] and Water [b]

Solute	Log Partition Coefficients (Molar Scale) at 25° (*SD*)			
	Shake-Flask		Filter Probe	
o-Chloroaniline	0.983	(0.012)	0.978	(0.021)
p-Chloroaniline	0.462	(0.012)	0.462	(0.019)
Methyl Benzoate	1.77	(0.046)	1.78	(0.056)
p-Nitrotoluene	1.97	(0.030)	1.92	(0.060)
p-Cresol	−0.395	(0.025)	−0.379	(0.019)

[a] 2,2,4-Trimethylpentane.
[b] Phosphate buffer pH 7.

for the examination of various environmental variables on the partitioning process.

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The filter-probe extractor was machined by H. van Ijzendoorn, and J. F. M. Kinkel, H. Wijnne, and P. Smit were involved in using and developing the total procedure.

BOOKS

Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. Edited by WILLIAM E. EVANS, JEROME J. SCHENTAG, and WILLIAM J. JUSKO. Applied Therapeutics, P.O. Box 31-747, San Francisco, CA 94131. 1980. 708 pp. 15 × 23 cm. Price $34.00.

As noted in the preface, this text is intended as a "source of the objective criteria and systematic approaches necessary for rational application of pharmacokinetics in clinical practice." The editors and authors have achieved that goal admirably. The text is primarily a compilation of information on specific drugs amenable to therapeutic monitoring and for which there is sufficient literature to permit a critical review. A particularly attractive approach is the inclusion of "counterpoint" discussions which accompany several chapters. These are intended to present another author's perspective when a consensus of opinion did not exist on that topic.

An introductory chapter is followed by a discussion (and a counterpoint presentation) of clinical pharmacokinetic consultation services and three chapters dealing with pharmacokinetics in renal and liver disease and in neonates. The remaining chapters are devoted to specific drugs and include: theophylline, aminoglycosides, cephalosporins, phenytoin, digoxin, lidocaine, procainamide, quinidine, propranolol, salicylates, methotrexate, tricyclic antidepressants, lithium, and heparin. Counterpoint discussions accompany the sections on theophylline, aminoglycosides, phenytoin, and lidocaine. The final chapter is concerned with guidelines for collection and the pharmacokinetic analysis of data.

Each chapter dealing with a specific drug contains the following major topics: introduction/background, absorption, distribution, elimination, concentration *versus* response and toxicity, clinical application of pharmacokinetic data, assay methods, and summary. Adhering to a common format enhances the readability of the text and permits the reader easy access to specific desired information. The chapters are concise, written well, and are replete with summary tables and figures. Each chapter has a substantial reference list and literature citations are current.

This book is unquestionably the best text of this type currently available. The editors by necessity have assumed a basic understanding in pharmacokinetics and as a result there are few expositions on fundamental principles and relatively few equations are employed. The reviewer believes this to be an advantage of the text.

A difficulty with publishing a compilation of this type is the fact that much of the material will become rapidly dated as a result of the literature explosion in the area of clinical pharmacokinetics. The editors are certainly aware of this and mention in the preface that this is the first edition. One presumes that others will follow. In subsequent revisions, the editors are encouraged to employ the approach for compiling clinical pharmacokinetic data as suggested by Sheiner *et al.* [*J. Pharmacokinet. Biopharm.*, **9**, 59 (1981)]. The text might also benefit from a table of symbols to be used uniformly throughout (and with common units, if possible).

The reviewer has no hesitation in recommending this text to pharmacy and medical practitioners who are involved in drug therapy and who are interested in improving theory. Pharmacy students in advanced courses, all Pharm.D. students, and clinical pharmacology fellows should consider this a most useful text.

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