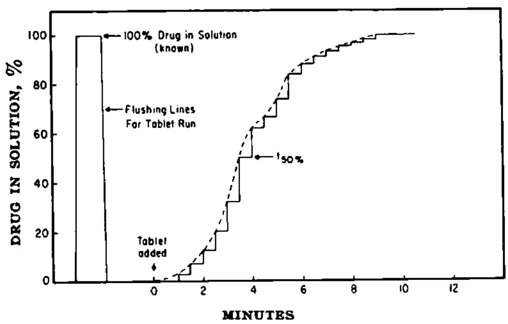

Fig. 3.—Idealized recorder curve obtained with modified continuous cycling method. Actual curves recorded at sufficiently fast chart speeds will show the vertical lines to be more nearly sigmoidal, due to the time lag involved in the establishment of optical density equilibrium. Dashed line indicates dissolution profile; vertical line indicates flow cell open; horizontal line indicates flow cell closed.

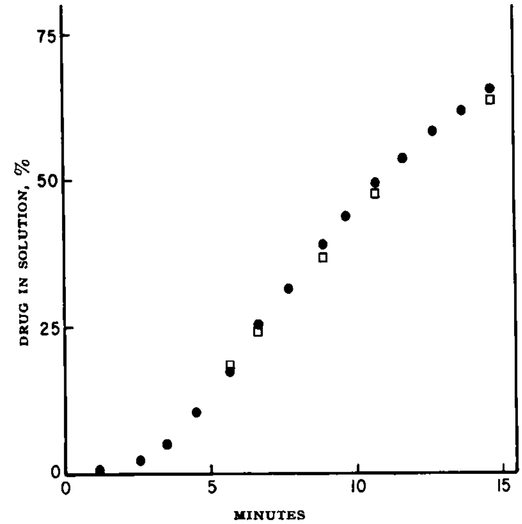

Fig. 4.—Dissolution profile of a sulfonylurea tablet obtained by the automated procedure and by simultaneous independent assay: ●, automated; □, independent assay.

RESULTS AND DISCUSSION

Vertical lines shown in the idealized recorder tracing in Fig. 3 represent the rapid change in recorder response which occurs when the sample stream is diverted through the flow cell at 1-minute intervals. Shortly after establishment of equilibrium in the lines, the rapidly flowing sample stream is once again shunted away from the filter and flow cell. During this time no sample flows through the cell; hence a horizontal trace is made by the pen until the valve once again opens to divert the sample stream through the filter and flow cell. Intersection of the horizontal and vertical lines represents a concentration of drug in solution at that time; the dissolution profile of the dosage form is shown by a dashed line joining these intersections or concentration-time values.

Accuracy and reliability of the modified continuous cycling method has been determined by simultaneous independent assays of the dissolution fluid during the dissolution process of various tablets. The dissolution profile of a sulfonylurea tablet in pH 7.2 buffer at 37° was determined in a series of studies conducted on different days by different investigators using the modified method described above and by simultaneous independent spectrophotometric assays of the dissolution fluid. Figure 4 is typical of the excellent agreement which exists between the automated and manual methods.

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Ferguson Principle and the Critical Micelle Concentration

By BERNARD ECANOW and FREDERICK P. SIEGEL

The thermodynamic activity values of a series of quaternary ammonium salts were calculated through the use of critical micelle concentrations. The correlation of these thermodynamic activities to the published values of their bactericidal activities is shown through application of the Ferguson principle. The value of the Ferguson principle in helping to point out the possible presence of different mechanisms of activity within a series of similar compounds has been suggested.

Ferguson (1) has suggested that the toxicities of physically toxic substances should not be compared by the values of the toxic concentrations in the external solution but by the chemical potentials in this phase, which must be identical with the chemical potential at the site of activity. Ferguson used the activity function of G.N. Lewis as the chemical potential. From a review of published data, he showed that "though diverse chemical compounds exert the same toxic effect on a given organism at widely different concentrations, the activities corresponding to these concentrations lie within a relatively narrow range. The differences in activity within this range are ascribed to the effect of chemical constitution."

It has been shown (1, 2) that when the toxic agent is applied as a vapor, the activity is given with "useful" accuracy by the ratio of the partial pressure of the agent over that of the saturated vapor pressure of the substance at the temperature

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TABLE I.—ACTIVITY OF QUATERNARY AMMONIUM COMPOUNDS

Quaternary Ammonium Chloride	CMC (N)	M. aureus Test Concn. $M \times 10^4$	M. aureus Killing Time[a], Min.	E. coli Test Concn. $M \times 10^4$	E. coli Killing Time[a], Min.	Activity M. aureus	Activity E. Coli
$C_{12}H_{25}N + (CH_3)_3$	0.0228	7.50	3.6	7.50	1.5	0.033	0.033
$C_{12}H_{25}N + (CH_3)_2(C_2H_5)$	0.0213	7.50	1.8	7.50	2.0	0.035	0.035
$C_{12}H_{25}N + (CH_3)(C_2H_5)_2$	0.0199	7.50	2.2	7.50	1.5	0.038	0.038
$C_{12}H_{25}N + (C_2H_5)_3$	0.0193	7.50	1.8	7.50	2.0	0.039	0.039
$C_{12}H_{27}N + (CH_3)_3$	0.0112	2.50	1.3	2.50	15	0.022	0.022
$C_{14}H_{29}N + (CH_3)_3$	0.0058	0.750	3.7	0.750	25	0.014	0.014
$C_{16}H_{33}N + (CH_3)_3$	0.0015	0.750	0.35	0.750	2.5	0.050	0.050
$C_{18}H_{37}N + (CH_3)_3$	0.000346	0.750	0.6	0.750	0.8	0.22	0.23
$C_6H_5—N + (CH_3)_2(C_{12}H_{25})$	0.00765	1.00	10.6	1.25	12.4	0.013	0.016
$C_6H_5—CH_2N + (CH_3)_2(C_{12}H_{25})$	0.0081	1.00	9.5	1.25	11.1	0.012	0.015
$C_6H_5—CH_2CH_2N + (CH_3)_2$-$(C_{12}H_{25})$	0.0041	1.00	0.73	1.25	9.4	0.024	0.030
$C_6H_5—CH_2N + (CH_3)(C_2H_5)$-$(C_{12}H_{25})$	0.0077	1.00	10.0	1.25	12.7	0.013	0.016
$CF_3C_6H_4—CH_2N + (CH_3)_2$-$(C_{12}H_{25})$	0.0032	1.00	0.37	1.25	6.0	0.032	0.039
$C_6H_5—(CH_2)_3—N + (CH_3)_2$-$(CH_{12}H_{25})$	0.00313	1.00	1.6	...	...	0.032	...

[a] Time required for 99.99% kill.

of the experiment. When the toxic agent is applied in solution and is a substance of limited solubility, the activity at the toxic concentration can be obtained (with sufficient accuracy for judicious use) by using the ratio of the toxic concentration of the substance over its solubility.

It is the purpose of this paper to show that the Ferguson principle can be extended to the relationship of bactericidal activity of quaternary ammonium salts and the critical micelle concentration (CMC) of the salts.

DISCUSSION

J. A. Cella, *et al.* (3), have reported that bactericidal activity generally appears to increase with decreased CMC within a series of quaternary ammonium salts that were tested. The data shown in Table I are from their work.

Previous investigators (1, 2, 4) have preceded with the selection of the pure substances as the standard free state and on the basis that solutions in equilibrium with excess solid have the same thermodynamic activity. An extension of this concept should apply to the equilibrium of solutions with micelles. The thermodynamic activity and, therefore, the biological activity should be equal to a constant per cent of the CMC of the active constituent.

The activities in Table I are calculated by obtaining the ratio of the test concentration divided by CMC. The variation between activity coefficients shown in Table I is very small (with one exception), showing a two- or three-fold difference as against the 200- to 300-fold variation in the extremes of CMC. As the Ferguson principle holds here, it tends to substantiate the view that the bactericidal activity is the result of some physical activity (presumably surface effects) rather than chemical activity.

In reviewing Table I without the columns of activity indices, one would have a difficult time discerning a striking difference in the activity of any compound. However, with the inclusion of the activities it becomes apparent that compound 8 has a unique value. Therefore, this would indicate that the compound may act through a different mechanism.

SUMMARY

The thermodynamic activity values of a series of quaternary ammonium salts were calculated through the use of CMC. The correlation of these thermodynamic activities to the published values of their bactericidal activities is shown through application of the Ferguson principle.

The value of the Ferguson principle in helping to point out the possible presence of different mechanisms of activity within a series of similar compounds has been suggested.

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