and, it also acts better in alcohol than in water. It may be noted that the alcohol incorporating either Tween 20 or Tween 80 extracts the drug almost equally. However, the solvent potentiated with Tween 80 acts more quickly in the beginning as evidenced by the values of per cent alkaloids extracted within short durations. Further, alcohol incorporating Tween 80 acts as a more selective solvent than that containing Tween 20 as indicated by the respective s.s.i. values (0.640 and 0.594).

DISCUSSION

The effect of two surfactants, Tween 20 and Tween 80, on the extraction of belladonna herb has been studied first by the percolation process (Tween 20 only) and then by the mechanical agitation process. It has been found, in both the processes, the solvent (alcohol) is potentiated by adding Tween 20 and permits the preliminary maceration for 24 hours to be eliminated. The purpose of maceration is to allow the drug to imbibe the solvent to facilitate the subsequent extraction. The most apparent effect of the use of the two Tweens in the solvent is that imbibition takes place so quickly that day-long maceration becomes unnecessary and the whole process is expedited.

Though both the surfactants were shown to be effective in potentiating the solvents, Tween 80 was superior to Tween 20 in the mechanical agitation process. This, probably, is due to the presence of the oleate radical, an 18-carbon chain, in the molecule of Tween 80. The laurate radical present in Tween 20 is only a 10-carbon group.

In the percolation process the potentiation of alcohol by Tween 20 has been found not to improve its solvent selectivity, but in the mechanical agitation process there is a marked enhancement. Both Tween 20 and Tween 80 have definitely higher s.s.i. values. The higher the value of this index, the higher will be the selectivity of the solvent, meaning that it extracts the active principles more than it does the other inert constituents.

CONCLUSIONS

Polyoxyethylene sorbitan monolaurate (Tween 20) and polyoxyethylene sorbitan mono-oleate (Tween 80) have been found to potentiate 70% alcohol and water as solvents in the extraction of belladonna herb (*A. belladonna*) by percolation and mechanical agitation processes. Tween 80 acts better than Tween 20 in the latter process. Both these surfactants act better in 70% alcohol than they do in water. In the percolation process the selectivity of the solvent (70% alcohol) is not improved but in the mechanical agitation process it is appreciably enhanced.

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Absorption and Excretion of Sulfadiazine After Subcutaneous Implantation of Disks in Rats

By BERTON E. BALLARD and EINO NELSON†

Thin, cylindrical disk-shaped pellets of sulfadiazine were subcutaneously implanted in rats and free and total urinary sulfadiazine excretion followed. It was possible to relate the mean pellet absorption rate per unit area to the mean excretion rate per unit area and to the fraction of a dose of the drug eventually excreted in the urine.

ABSORPTION of drugs from implants may be studied by following urinary excretion of the unchanged drug, its metabolite(s), or both, by determination of drug blood level, by following excretion of substances such as electrolytes that reflect the drug's action in the body, by studying drug action on a target organ, or by following the decrease in weight of the implants themselves. In previous work it has been shown that the rate-limiting step in absorption after subcutaneous implantation of a number of drugs was the dissolution process at the absorption site (1). The work reported now gives the results of experiments which were conducted to determine the relationship between cumulative urinary excretion of sulfadiazine and acetylated sulfadiazine and change in surface area of thin, cylindrical disks of this material after subcutaneous implantation in rats. A study of this type has not been previously conducted using cylindrical implants; sulfadiazine serves as a readily available and assayable model compound.

PROCEDURE

Thin, cylindrical disks of compressed drug grade sulfadiazine were prepared and subcutaneously implanted in a manner and site described before (1). Four weighed disks were implanted into each of three Sprague-Dawley rats of both sexes designated as A, B, and C, having weights of 210, 335, and 410 Gm., respectively. They were placed in separate glass metabolism cages from which the urine was collected twice daily for 5 days. The urine was assayed for free and total sulfadiazine

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by the Bratton and Marshall method (2). A Bausch and Lomb Spectronic 20 colorimeter was used in the application of the method.

The final mean weights of the disks were corrected for the weight of the proteinaceous "ghost" described by Folley (3) in the following way. A 0.4190-Gm. sample of most of the remains of disks removed from rats A, B, and C was dissolved in dilute ammonium hydroxide. The clear solution was decanted from the "ghost" residues and several portions of distilled water were added and decanted. The small amount of water remaining containing the "ghost" was then evaporated to dryness at room temperature. The residue weighed 3 mg. Thus, the final weight of the disks as yet uncorrected for "ghost" weight was heavy by slightly more than 0.71%. The observed final mean weights in Table I were corrected for the weight of the "ghost."

RESULTS

Table I shows for rats A to C data on the properties and dimensions of the disk-shaped pellets before and after implantation. The initial and final mean disk areas were graphically estimated by a method described previously which used for illustration some of the data given here for rat A (4). The cumulative amounts of free and total sulfadiazine excreted in the urine for the three animals appear in Table II, along with the fraction, f, of total drug recovered in a time infinite in terms of the experiment which was about 147 hours. The nature of the type of cumulative drug excretion curves obtained is shown in Fig. 1 which was constructed from data obtained from rat A. It should be noted that on the cumulative excretion curve only the high points should be considered in the plot, because low points may be due to collection time not corresponding to the last voiding time.

DISCUSSION

There are only a few reports in the literature where the urinary excretion of drug or metabolite(s) have been followed subsequent to drug implantation (5–11). However, except in one of these studies, no attempts were made to relate the absorption rate of implants to urinary excretion rate of drug or metabolite(s) (5).

Theoretically, if the cumulative amount of drug and its metabolite(s) excreted in the urine is plotted against time, one should note a line with a progressively decreasing slope, indicating that the ex-

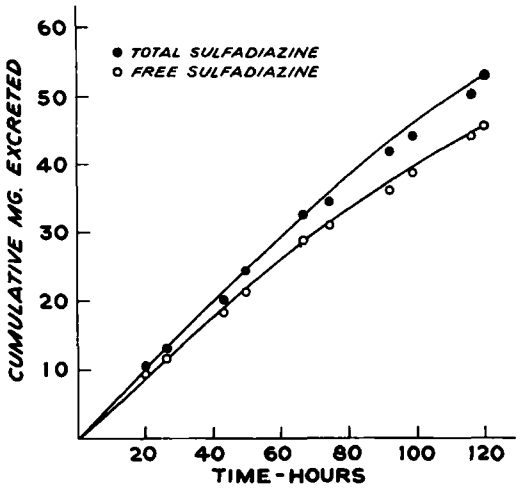

Fig. 1.—Illustrating the nature of the cumulative free and total sulfadiazine excretion *vs.* time curve after subcutaneous implantation of cylindrical disks of drug (Rat A).

TABLE I.—SULFADIAZINE PELLET IMPLANT DIMENSIONS AND PROPERTIES BEFORE AND AFTER IMPLANTATION

Dimension or Property[c]	Rat A[a]		Rat B		Rat C	
	Initial	Final	Initial	Final	Initial	Final
Height, cm.	0.1133	0.0892	0.1196	0.0998	0.1031	0.0846
Diameter, cm.	0.637	0.618	0.637	0.618	0.636	0.621
Weight, Gm.	0.0508	0.0342[b]	0.0531	0.0378[b]	0.0458	0.0319[b]
Estimated area, cm.^{2}	0.864	0.740	0.876	0.761	0.841	0.733
Apparent density, Gm./cm.^{3}	1.407	...	1.405	...	1.401	...
Implantation time (hr.)	...	119.2	...	119.2	...	118.3
$\bar{R}/\bar{A} \times 10^4$ Gm./hr./cm.^{2}	1.74		1.57		1.49	

[a] Data for this animal have been previously presented in connection with a graphic method for estimating mean initial and final implant areas (4). [b] Weight corrected for weight of "ghost." [c] Means of the four thin, cylindrical disks implanted in a given rat.

TABLE II.—CUMULATIVE SULFADIAZINE EXCRETION IN MG. AFTER DRUG IMPLANTATION[a]

Rat A			Rat B			Rat C		
Time, hr.	Free	Total	Time, hr.	Free	Total	Time, hr.	Free	Total
19.2	9.4	10.4	18.8	7.2	9.2	18.3	3.0	3.6
26.2	11.5	12.9	26.0	9.2	11.8	25.8	5.6	7.2
43.0	18.2	20.2	42.8	14.9	20.8	42.2	12.4	15.8
49.2	21.2	24.1	48.8	17.6	24.0	49.1	15.6	20.0
67.3	29.0	32.2	67.2	24.2	31.6	67.1	18.6	24.2
74.6	30.8	34.5	74.3	26.5	34.5	74.2	21.3	27.7
92.2	36.7	41.5	92.0	32.2	41.0	91.6	25.6	33.3
98.4	38.6	44.1	98.2	34.3	43.8	97.9	28.1	36.7
116.4	44.0	50.7	116.2	38.2	48.7	116.0	30.8	40.2
118.9	45.9	52.8	119.1	40.4	51.6	118.0	32.2	42.0
119.2	...	...	119.2[b]	...	...	118.3[b]	...	...
147.1	...	55.6	146.8	...	54.8	146.5	...	45.0

[a] Fractions of doses recovered for Rats A, B, and C were, respectively, 0.837, 0.896, and 0.809. [b] Time at which implants were removed.

cretion rate diminishes with time. This decrease in excretion rate should parallel the decrease in absorption rate of the implant because of area changes which occur during absorption. When such a plot is made from the data presented in Table I of Latven and Welch (9), a decrease in excretion rate with time is observed. However, it cannot be determined from their data the values of the initial and final areas of the implants. Further, it should be possible to equate implant absorption rate to the urinary excretion rate of free and metabolized drug when implant surface area and fraction of the total dose recovered are considered and when absorption is solution rate limited.

An animal implanted with a drug pellet of a geometric form such that only small decreases in area occur with absorption may be likened to one given a continuous infusion of a drug when absorption from implant is solution rate limited. For the infused animal the relationship

$$Ri = Re/f \qquad \text{(Eq. 1)}$$

should apply after equilibrium is established, assuming drug removal processes are first order which is the usual case, where Ri is the constant rate of infusion, Re is the rate of urinary excretion, and f is the fraction of the total dose excreted in the urine in a time infinite in terms of the experiment. A similar relationship should hold in the case of implants after surface area corrections are made. Then the mean absorption rate per mean area, $\bar{R}/\bar{A}$, should equal the mean excretion rate per mean area, $\overline{Re}/\bar{A}$, divided by the fraction, f

$$\bar{R}/\bar{A} = (\overline{Re}/\bar{A})/f \qquad \text{(Eq. 2)}$$

assuming that no deposition of drug occurs at another site (*i.e.*, the kidney) (12, 13).

$$\bar{R}/\bar{A} \text{ per pellet} = \frac{(W_i - W_f)/t_i}{(A_i + A_f)/2} \qquad \text{(Eq. 3)}$$

$$\overline{Re}/\bar{A} \text{ per pellet} = \frac{(W_e/N)/t_e}{(A_i + A_f)/2} \qquad \text{(Eq. 4)}$$

where W_i and W_f are the initial and final mean pellet weights, t_i is the time of implantation, A_i and A_f are the initial and final areas of the implant, W_e is the weight of total drug recovered in the urine in time t_e, N is the number of pellets used, and t_e is the time of excretion.

TABLE III.—MATERIAL BALANCE: SHOWING THAT $\bar{R}/\bar{A} \cong (\overline{Re}/\bar{A})/f$

Rat	$\bar{R}/\bar{A}$ Gm./hr./cm.²	$(\overline{Re}/\bar{A})/f$ Gm./hr./cm.²
A	1.74×10^{-4}[a]	1.66×10^{-4}[b]
B	1.57×10^{-4}	1.47×10^{-4}
C	1.49×10^{-4}	1.40×10^{-4}

[a] $\bar{R}/\bar{A}$ per pellet $= \dfrac{(Wi - Wf)/ti}{(Ai + Af)/2} = \dfrac{(0.0508 - 0.0342)/119.2}{(0.864 + 0.740)/2} = 1.74 \times 10^{-4}$

[b] $(\overline{Re}/\bar{A})/f$ per pellet $= \dfrac{(We/N)/te}{(Ai + Af)/2}/f = \dfrac{(1/4 \times 0.0528)/118.9}{(0.864 + 0.740)/2}/0.837 = 1.66 \times 10^{-4}$

Table III shows the agreement between the experimental values of $\bar{R}/\bar{A}$ and $(\overline{Re}/\bar{A})/f$. Similar agreement was also observed when a different method of calculating $\overline{Re}/\bar{A}$ was used (13). The value of the $(\overline{Re}/\bar{A})/f$ is slightly smaller than that for $\bar{R}/\bar{A}$. This is expected since time in the beginning of the experiment is required for the establishment of equilibrium in drug absorption, distribution, metabolism, or excretion of drug; *i.e.*, t_e by this method is slightly larger than it should be.

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A Field Method for Alkaloid Screening of Plants

By C. C. J. CULVENOR and J. S. FITZGERALD

An alkaloid screening procedure is described which is suitable for use in the field with fresh plant material and can be carried out in a sufficiently short time to enable a chemist to keep pace with a collecting botanist.

IN VIEW of a strong world-wide interest in the discovery and isolation of new plant alkaloids, the following observations on a simple screen test suitable for field use may be of value. The method was designed for use by a botanist-chemist team collecting in remote and sparsely settled areas not previously explored for alkaloid-bearing plants. In making a test in the field under these circumstances there are great advantages: only positive samples need be collected, thus avoiding drying and despatch of most of the new species encountered; and samples giving strongly positive tests can be collected in bulk immediately, eliminating the need to revisit the area for this purpose. To achieve these advantages, a species should be tested when first encountered rather than collecting and keeping it until camp is set up in the evening. Thus, speed of operation and simplicity of procedure are essential. The

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