concentration on absorption. Present research is proceeding along these lines.

REFERENCES

(1) N. K. Patel and H. B. Kostenbauder, *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 289(1958).

(2) G. Levy and T. Matsuzawa, *J. Pharm. Sci.*, **54**, 1003(1965).

(3) R. H. Reuning and G. Levy, *ibid.*, **56**, 843(1967).

(4) C. W. Whitworth, *ibid.*, **54**, 463(1965).

(5) C. W. Whitworth and L. D. Yantis, *ibid.*, **56**, 1661(1967).

(6) G. Levy and J. A. Anello, *ibid.*, **57**, 101(1968).

Calculations of Release Rates From Sustained-Release Dosage Forms Using the Wiley Method

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Abstract ☐ In the Wiley method for determining release rates from sustained-release formulations, typically, each hourly sample is assayed. If release specifications include intervals of more than 1 hr., a method is presented by which samples can be combined in a manner such that it is not necessary to assay each hourly sample. In cases where the assay is tedious or difficult, or in cases where multiple assays are necessary, this procedure may result in a substantial saving of time.

Keyphrases ☐ Release rates—sustained-release dosage forms ☐ Wiley method—release rate calculations ☐ Sample combination— release rates

Among the methods proposed and described in the literature for *in vitro* testing of release rates from sustained-release formulations are those which rely on hourly assay samples taken from a continuous extraction solvent (1–6). One such procedure, in current use, was originally proposed by Wiley (1). The material to be assayed is packed in a specially designed column and 100 ml. of simulated gastric fluid is circulated through the column by means of a pump. After each hour, 50 ml. of fluid is removed for assay and replaced with 50 ml. of simulated intestinal fluid. Thus, the ratio of intestinal to gastric fluid in the extracting solvent is increased with each succeeding hour. Since the calculation of total amount released during a given hourly interval is dependent on the assay of the previous hourly sample, (*vide infra*), release rates are generally calculated for each hour. This paper is concerned with a method by which release rates can be determined over intervals of more than 1 hr. without assaying each and every individual hourly sample.

METHOD AND THEORY

If the method, as described above is used, the calculation for drug released during hour $(n-1)$ to (n) is $C_n = A_n - \frac{1}{2} A_{n-1}$, where A_n = assay of total active ingredient per 100 ml. of solution after hour (n).[1]

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[1] Since only 50 of 100 ml. of solution are taken for assay, the total amount of active ingredient in the sample, A_n, will be twice the amount found in the 50 ml.

Example 1:

Hr.	C_n	A_n
1	$C_1 = 10$	$C_1 = 10 = A_1$
2	$C_2 = 31$	$C_2 + \frac{1}{2} A_1 = 36 = A_2$
3	$C_3 = 12$	$C_3 + \frac{1}{2} A_2 = 30 = A_3$

e.g., $C_3 = A_3 - \frac{1}{2} A_2 = 30 - \frac{1}{2} (36) = 12$

Suppose that one is not interested in the quantity released each and every hour, but, rather, between certain specified hours, *e.g.*, between Hours 1 and 3. The question is: is it necessary to assay the samples obtained during the intermittent hours, *e.g.*, Hour 2, in order to calculate the total amount released during, *e.g.*, Hours 2 and 3? Remember that the fluid must still be changed every hour.

If hourly samples are properly combined, it is not necessary to separately assay the samples from intermittent hours. Consider Example 1. If 25 ml. of the Hour 2 sample is combined with 50 ml. of the Hour 3 sample and assayed, the total calculated amount of active material released will be $(C_3 + \frac{1}{2} A_2) + (\frac{1}{2} A_2) = C_3 + C_2 + \frac{1}{2} C_1$. Thus, with a knowledge of C_1, $C_3 + C_2$ may be calculated.[2]

In general, the solution to the problem is not as simple as in the above example. Fortunately, there exists a rather straightforward solution to the problem of mixing samples and the calculation of the amount released between specified hours as follows:

Indicate hours at which time release limits are specified, *e.g.*, 1, 3, 6, and 7 hr., *i.e.*, one wishes to know the amount released after 1 hr., amount released between 1 and 3 hr., between 4 and 6 hr., and 6 and 7 hr. These hours would be called (1, 3, 6, 7) assay hours for convenience.

When hourly samples are combined, the samples collected at assay hours will never be combined with each other. Save all hourly samples (50 ml. in the present case) in numerical order and combine as follows:

To each assay hour sample, first add one-half the quantity of the previous hourly samples until another assay hour sample is reached. Ignore this sample and then proceed to add one-fourth the quantity of the next prior hourly samples until another assay hour sample is reached. Then add one-eighth of the prior samples, *etc*. Note that the fraction of samples added decreases in integral powers of $(\frac{1}{2})$ and that if two successive assay hours are encountered, the addition of the prior samples is decreased by one-half for each assay hour encountered.

The following two examples should clarify the above procedure. H_n refers to the solutions removed for assay after hour (n).

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[2] For this and subsequent calculations, when samples are combined, the combined sample is treated as having a volume of 50 ml. Thus, to calculate the total amount in 100 ml., the amount found in the combined sample should be multiplied by 2. For example, if 24 mg. is found in a combined 75-ml. sample, 48 mg./100 ml. is calculated.

Table I—Assay Hours are 1, 3, 4, 6, 7

Hour	mg. Released (C_n)	Assay[a] (A_n)	Combined Sample	Combined Sample Assay	Calculations
I	10	10	(I)	10	10
II	31	36			
III	12	30	(III) + $\frac{1}{2}$ (II)	48	$48 - \frac{1}{2}(10) = 43 = C_2 + C_3$
IV	33	48	(IV) + $\frac{1}{4}$ (II)	57	$57 - \frac{1}{2}(48) = 33 = C_4$
V	16	40			
VI	14	34	(VI) + $\frac{1}{2}$ (V) + $\frac{1}{8}$ (II)	58.5	$58.5 - \frac{1}{2}(57) = 30 = C_5 + C_6$
VII	24	41	(VII) + $\frac{1}{4}$ (V) + $\frac{1}{16}$ (II)	53.25	$53.25 - \frac{1}{2}(58.5) = 24 = C_7$

[a] These are the results expected, if samples would be assayed each hour.

Example 2: assay hours = 1, 3, 6, 7.

Hr.	Combination
1	H_1
3	$H_3 + \frac{1}{2} H_2$
6	$H_6 + \frac{1}{2} H_5 + \frac{1}{2} H_4 + \frac{1}{4} H_2$
7	$H_7 + \frac{1}{4} H_5 + \frac{1}{4} H_4 + \frac{1}{8} H_2$

Example 3: assay hours = 1, 2, 4, 5, 7.

Hr.	Combination
1	H_1
2	H_2
4	$H_4 + \frac{1}{2} H_3$
5	$H_5 + \frac{1}{4} H_3$
7	$H_7 + \frac{1}{2} H_6 + \frac{1}{8} H_3$

The calculations are simple. Calculate the active ingredient in the combined sample for the assay hour in question, ignoring volume changes (to calculate combined sample assay, multiply the total amount found in the combined sample by two see *Footnote 2*). Subtract from this result one-half of the assay result observed in the next prior combined sample. The difference is the total amount released during the interval in question. In Example 2, the amount released during Hours 4–6 would be the combined assay in Hour 6 less one-half the combined assay in Hour 3.

A fully worked out example appears in Table I (Example 4).

Proof—One has assay samples, A_i, corresponding to X_i, the amount released during Hour i, such that $X_i = A_i - \frac{1}{2} A_{i-1}$.

Arrange all A consecutively and divided into intervals I_j. Let n_j represent the number of assay samples in interval j, *i.e.*, samples in interval j are $1j, 2j, 3j \ldots n_j$. Thus, A_{nj} represents the last sample in interval j; A_{1k} represents the first sample in interval k.

Let Y_j be the combined assay sample from interval j, where

$$Y_j = A_{nj} + \sum_{k=1}^{j} \sum_{i=1k}^{n_k-1} (\tfrac{1}{2})^{j-k+1} A_{ik}$$

The procedure described in the paper may be stated as:

$$I_j = Y_j - \tfrac{1}{2} Y_{j-1} = A_{nj} + \sum_{k=1}^{j} \sum_{i=1k}^{n_k-1} (\tfrac{1}{2})^{j-k+1} A_{ik} -$$

$$\tfrac{1}{2} \left[A_{n_{j-1}} + \sum_{k=1}^{j-1} \sum_{i=1k}^{n_k-1} (\tfrac{1}{2})^{j-k} A_{ik} \right] \quad \text{(Eq. 1)}$$

By definition,

$$I_j = Y_j - \tfrac{1}{2} Y_{j-1} = \sum_{i=1j}^{nj} X_i = \sum_{i=1j}^{nj} (A_i - \tfrac{1}{2} A_{i-1}) =$$

$$A_{nj} + \tfrac{1}{2} \left[\sum_{i=1j}^{nj-1} A_i \right] - \tfrac{1}{2} A_{n_{j-1}} \quad \text{(Eq. 2)}$$

Thus, we must prove that Eq. 1 = Eq. 2. Eq. 1 may be written as:

$$A_{nj} + \tfrac{1}{2} \left[\sum_{i=1j}^{nj-1} A_i \right] + \tfrac{1}{2} \left[\sum_{k=1}^{j-1} \sum_{i=1k}^{n_k-1} (\tfrac{1}{2})^{j-k} A_{ik} \right] -$$

$$\tfrac{1}{2} \left[A_{n_{j-1}} + \sum_{k=1}^{j-1} \sum_{i=1k}^{n_k-1} (\tfrac{1}{2})^{j-k} A_{ik} \right] =$$

$$A_{nj} + \tfrac{1}{2} \left[\sum_{i=1j}^{nj-1} A_i \right] - \tfrac{1}{2} A_{n-1} = \sum_{i=1j}^{nj} X_i = \text{Eq. 2.}$$

Q.E.D.

SUMMARY

An approach has been described wherein release rates for sustained-release formulations covering intervals greater than 1 hr. can be calculated without assaying each hourly sample when a continuous extraction method is employed. This method saves a substantial amount of time when the assay is laborious and/or multiple assays are required at each time interval.

REFERENCES

(1) F. Wiley, personal communication, distributed to the Combined Pharmaceutical Contact Committee of the ADMA and APMA, October 10–11, 1957.

(2) R. H. Blythe, *Drug. Std.*, **26**, 1 (1958).

(3) R. A. Nash and A. D. Marcus, *ibid.*, **28**, 1(1960).

(4) E. B. Vliet, *ibid.*, **28**, 113(1960).

(5) J. Lazarus and J. Cooper, *J. Pharm. Sci.*, **50**, 715(1961).

(6) E. O. Kruger and E. B. Vliet, *ibid.*, **51**, 181(1962).

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