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Correction of raw dissolution data for loss of drug and volume during sampling

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Received 18 November 1996

Accepted 20 March 1997

The communication reports the derivation of relationships that can be directly applied to correct raw dissolution data for loss of drug and/or volume reduction during manual sampling in with replacement and without replacement studies.

DURING multi-point dissolution studies, a small aliquot is withdrawn at predetermined time intervals from the dissolution medium. The withdrawal of the sample not only causes a progressive decrease in the total dissolution medium, it also results in a cumulative loss of drug with each sample. Both these effects cause an error in the data obtained during without- replacement (WOR) studies, where the sample drawn is not replaced by an equal quantity of fresh medium. In the with-replacement (WR) studies, the volume is adjusted back to the original after each sampling and the error accrues in this case from the loss of drug only.

The dissolution data, in case of both WOR and WR studies, is hence required to be corrected for the error due to the loss of drug and/or change in the total medium volume. The correction can be applied mathematically to either raw absorbance (or concentration) data that are obtained directly on analysis of dissolution samples, or the derived amount (or percent) released values. The application of correction to the former is, however, advantageous as it provides freedom to calculate the derived amount, fraction or percent drug released values to the requirements of the user.

The factors for correction of derived values of amount (or percent) drug dissolved in WOR studies have been reported in literature[1]. In this communication we extend the reported relationships to calculate factors for correction of raw absorbance (or concentration) data obtained using either WOR or WR studies.

The formula described for calculation of corrected amount of drug dissolved, after the nth sample (1) is as follows:

* **For Correspondence**

$C_n \times V_n + \Sigma_{i=1}^{n-1} C_i \times V_s$ ..... (1)

Where C_n and V_n are the drug concentration and volumes of dissolution medium, respectively, at the nth sample. C_i is the concentration at the ith time point and V_s is the sample volume. Similarly, the formula for calculating the corrected value of percent drug dissolved (A_n) at nth time point is proposed to be as follows:

$$A_n = \overset{\circ}{A}n + \Sigma_{i=1}^{n-1} \overset{\circ}{A}i \times V_s/V_i \quad \text{..... (2)}$$

Where $\overset{\circ}{A}_i$ is the measured percent drug dissolved at time point i, corrected for volume.

The factors for correction of raw absorbance (or concentration) data may be derived from eq 1 by substituting volume of dissolution medium present in the chamber at nth sampling, i.e., V_n by $[V_t - \{(n-1) \times V_s\}]$, where V_t is the total volume of dissolution medium employed in the beginning of the dissolution run:

$$Amt_{corr} = C_n \times [V_t - \{(n-1) \times V_s\}] + \Sigma_{i=1}^{n-1} C_i \times V_s \quad \text{..... (3)}$$

Where Amt_{corr} is the corrected amount of drug. This equation on division by V_t throughout results in the following:

$$\frac{Amt_{corr}}{V_t} = \frac{C_n x[V_t - n-1) \times V_S}{V_t} + \left[\Sigma_{i=1}^{n-1} C_i \times \frac{V_s}{V_t}\right] \quad \text{..... (4)}$$

On rearranging eq 4, and representing the left hand side terms of corrected concentration ($Conc_{corr}$d), one gets:

$$Conc_{corr} = C_n + \frac{V_s}{V_t} [\Sigma_{i=1}^{n-1} C_i - (n-1) \times C_n] \quad \text{..... (5)}$$

A more simplified form is obtained on addition of C_n to the first term in brackets and on subtracting the same from the second term:

$$Conc_{corr} = C_n + [\frac{V_s}{V_t} \Sigma_{i=1}^{n} C_i - n \times C_n] \quad \text{..... (6)}$$

In accordance with this relationship, the addition of $V_s/V_t[\Sigma^n{}_{i=1} C_i - n \times C_n]$ to the observed data (C_n) would result in corrected concentration values. Analogously, the second term on the right side of eq 7 constitutes the correction factor which when added to observed absorbance values (Abs_n) leads to the corrected (Abs_{corr}) values:

$$Abs_{corr} = Abs_n + \frac{V_s}{V_t} [\Sigma_{i=1}^{n} Abs_i - n \times Abs_n] \quad \text{..... (7)}$$

The four eqs 1, 2, 6 and 7 account both for volume reduction and drug loss due to sampling, in each single formula. Hence these equations, in the form given, are applicable directly only to WOR studies where dissolution medium equal to the volume of sample withdrawn is not replaced.

A similar set of equations is derived for WR studies by substituting the parameter V_n in eq 1 by V_t, which is possible in this case as the total medium remains unchanged during the entire dissolution run. This simple substitution yields in a relationship that applied to correction of amount of drug dissolved after the nth sample :

$$Amt_{corr} = C_n \times V_t + \Sigma_{i=1}^{n-1} C_i \times V_s \quad \text{..... (8)}$$

A further division of eq 8 by V_t results in a formula applicable to correction of the raw concentration data obtained during a WR study:

$$Conc_{corr} = C_n + \frac{V_s}{V_t} \times \Sigma_{i=1}^{n-1} C_i \quad \text{..... (9)}$$

The corresponding equation for correction of raw absorbance data is as follows :

$$Abs_{corr} = Abs_n + \frac{V_s}{V_t} \times \Sigma_{i=1}^{n-1} Abs_i \quad \text{..... (10)}$$

The second term on the right side in eqs 8, 9 and 10 thus constitutes the factors for correction of various types of data available from a WR study.

Equations 6 and 7 describe the correction factors for raw absorbance and concentration data obtained during a WOR study while eqs 10 and 9 apply, respectively, to similar data obtained during WR studies. The reporting of the correction factors for raw data, especially for WOR studies, assumes

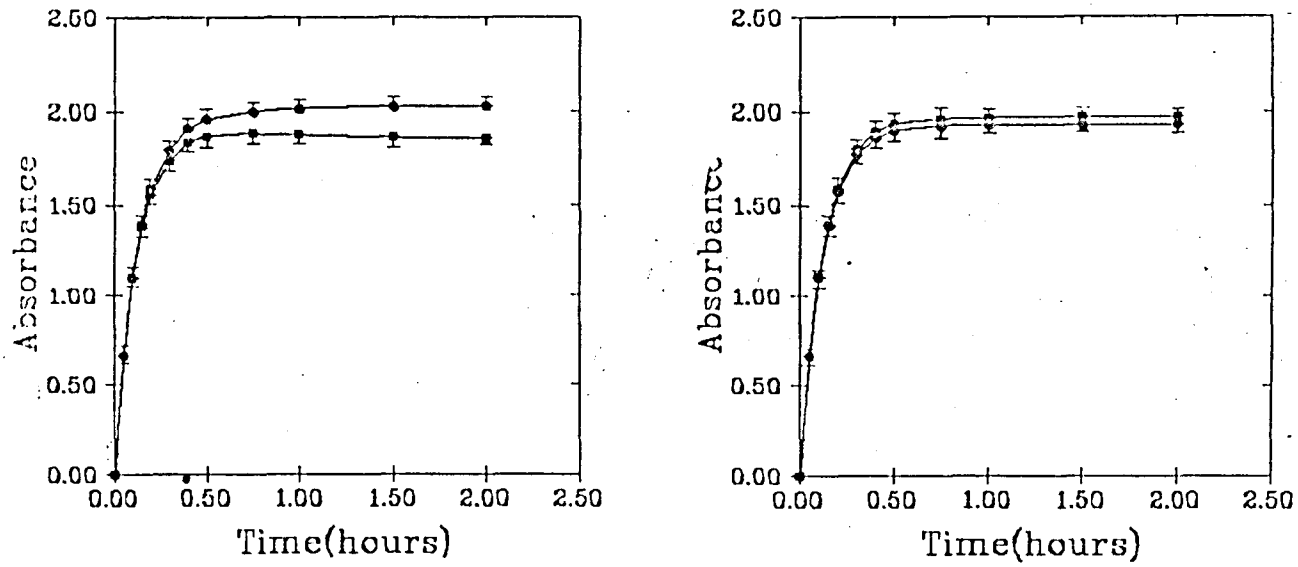

Fig 1: Graphical representation of dissolution data on conventional diclofenac tablet formulations at varied time intervals (n=10) depicting influence of correction factors using (a) WR and (b) WOR sampling methods. The solid circles and solid squares, depict the corrected and uncorrected observations, respectively while crossbars indicate Mean ± S.D.

significance as they are not previously reported in literature and their derivation from eq 1 evidently is not very direct.

An interesting observation made on a critical study of eqs 1,2 and 6,7 is that the correction effect shall be opposite for raw concentration (or absorbance) data as compared to derived amount (or percent) values. In eqs 6, 7 there exists a negative term on the right side which apparently is absent in case of eqs 1, 2. Since the quantity C_n (or Abs_n) will always be greater than C_i (or Abs^i) in eqs 6, 7 the two assume corrected measured concentration (or absorbance) data to be lower than the uncorrected ones. Equations 1, 2 on the other hand predict the corrected amount (or percent amount) values to be higher than the uncorrected data. The opposite behaviour in the two situations accrues from the reduction in volume of dissolution medium on sampling, which in case of concentration (or absorabance) data results in overestimation of the raw values, and in case of total amount (or percent amount) data causes underestimation of the measured data, since the latter are dependent on total volume. Interestingly, such differential effect is not seen between eq 8 and eqs 9, 10 applicable to WR studies since herein the total volume always remains constant.

To validate the proposed correction factors, using WR and WOR sampling, dissolution studies (n=10) were carried out on diclofenac sodium tablet formulations in phosphate buffer (pH 6.8) using paddle method (Pharmatest dissolution tester PTW2, USA). The drug was analyzed spectrophotometrically (Spectronic 1201, UK) at 275 nm following appropriate dilution. The studies were conducted upto a period of 2 h for conventional (50 mg) and 14 h for the extended release (ER, 100 mg) tablet dosage forms. The absorbance-time plots for conventional formulations by WR and WOR sampling are shown in Fig. 1(a) and Fig 1(b), respectively, while those of ER formulations in Fig. 2(a) and Fig. 2(b), respectively. The figures clearly demonstrate the significant positive and negative influence of corrections on dissolution data obtained through WR and WOR

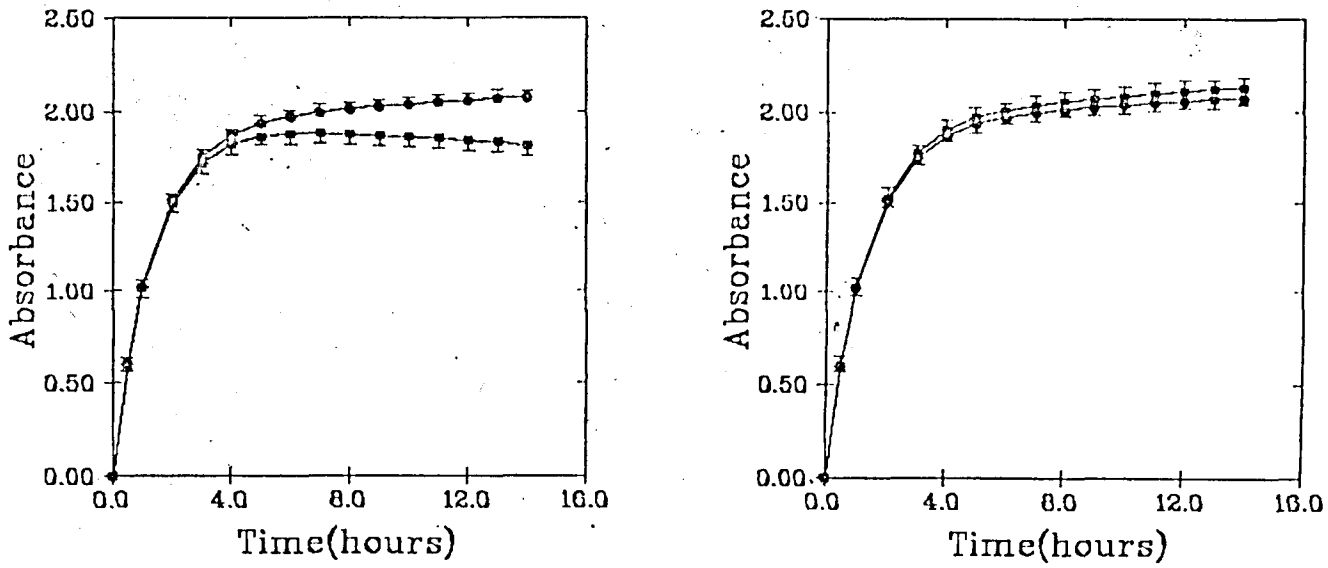

Fig. 2: Graphical representation of dissolution data on extended release diclofenac tablet formulations at varied time intervals (n=10) depicting influence of correction factors using (a) WR and (b) WOR sampling methods. The solid circles and solid squares, depict the corrected and uncorrected observations, respectively while crossbars indicate Mean ± SD.

studies, respectively. However, the amount of deviation between corrected and uncorrected observations tends to be greater in WR studies following multiple sampling. This is particularly true in case of ER formulations (Fig. 2) indicating even greater necessity of correction.

The application of correction factor to the voluminous dissolution data, usually obtained during formulation development and quality evaluation studies, using a hand-held calculator proves not only tedious, but also time consuming and error-prone. For the benefit of the readers, we list below a simple computer subprogram in FORTRAN, which can be made use of to get speedier and accurate calculations of the corrected values:

```
SUBROUTINE FACTOR (N, VT, VS, CN, CORCN)
REAL CN(20), CORWR (20), CORWOR(20),
+ SIGMA(20)
    DO 44 I=1, N
    SIGMA(I)=0.
44  CONTINUE
    VOLRATIO=VS/VT
    DO 55 I=1, N
    SIGMA(I) = SIGMA (I-1) + CN (I)
    CORWOR(I) = CN(I) + VOLRATIO* (SIGMA(I) - I*CN(I))
    CORWR(I) = CN(I) + VOLRATIO* SIGMA(I-1)
55  CONTINUE
    RETURN
    END.
```

The subroutine applies to correction of raw concentration data in accordance with eq 6 and 9, and can easily be adapted for correction of raw data as per eqs 7 or 10.

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