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Comparison of in vitro dissolution profiles by calculating mean dissolution time (MDT) or mean residence time (MRT)

Fridrun Podczeck

Department of Pharmaceutics, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX (UK)

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Summary

The technique of calculating the statistical moments of MDT or MRT is commonly used to describe in vitro drug release profiles, especially those for dissolution controlled release products. Any mathematical method used to calculate these values must be able to differentiate curves of different shape and extent, and should have a minimum of errors. Seven methods, which are described in the literature, have been compared in terms of their applicability to characterize different model release profiles. The mean error of the values calculated was determined. Only two methods, which calculate MRT values, appear to be useful. These are the pragmatic plane geometry using the residence profile and the overlapping parabolic integration. Pragmatic plane geometry for calculating MDT values provides exact estimates, if a complete zero order release profile is investigated. In general, the applicability of all the methods is limited by the error and the ability to differentiate between curves, especially for zero order kinetics release, if values for a complete drug release are not available.

Introduction

The drug dissolution from a dosage form plays an important role in the development of new drug formulations, especially controlled release dosage forms. The drug release is a function of time involving a series of processes, which can exist in a dosage form. An interrelationship between these processes can exist, but is very difficult to identify. The dissolution profile of a dosage form can be ascertained statistically by measurement of the amount of the drug substance dissolved in the dissolution liquid. The main important step is to determine the time function itself and to describe exactly this function by useful parameters. Pharmacopoea standards usually define a percentage limit dissolved at a fixed time. Alternatively, the time for 50% of the drug to appear in solution can be used. Both these approaches are single point measurements and do not adequately characterize the whole dissolution process. Attempts to use standard reaction kinetics equations rarely result in an adequate quantification of the total dissolution profile. Alternatively, the cumulative release profile is used to display the dissolution function. In the cumula-

Correspondence to: F. Podczeck, Dept of Pharmaceutics, The School of Pharmacy, University of London, Brunswick Square, London WC1N 1AX, U.K.

tive release profile the y value of each measurement represents the amount of drug substance, which must be dissolved in the dissolution liquid earlier than the corresponding time value identifies. This can be considered as a probability, which describes the time of residence of the drug substance in the dosage form. A dissolution profile may, therefore, also be regarded as distribution function of the residence times of each drug substance molecule in the pharmaceutical formulation.

Every distribution function can be described mathematically by the measures of central tendency and the measures of dispersion (Hays, 1973). These measures are based on the moments of first and second degree of a distribution function. For the normal distribution the moment of first degree is equal to the arithmetic mean value, and the moment of second degree is similar to the variance of the distribution. Using the moments of third and fourth degree the skewness and the kurtosis of the distribution function is calculable. Unfortunately, most dissolution profiles are not distributed normally. Wagner (1969) suggested that a log-normal distribution provided a logical distribution based on the availability of surface area during the dissolution process, associated with disintegrating proportions. Controlled release preparations would not have dissolution profiles, which would be expected to follow this type of distribution. Hence a method is required, which is not dependent on the type of the dissolution function.

The arithmetic mean value of any dissolution profile is called 'mean dissolution time' (MDT). If the content of the drug substance, which is still in the dosage form, is plotted as a function of time, the arithmetic mean value of the so-called residence profile is the 'mean residence time' (MRT) of the drug substance molecules in the dosage form. The technique of calculating statistical moments should be highly sensitive to changes in the distribution function. It is, however, only a mathematical model and has the common limitations, which belong to each model. The quality of the adaption of the values measured on the model depends on the numerical errors, which arise in the calculation. Therefore, the numerical errors must be controlled and should be as small as possible. One important source of errors is the fact that often 100% dissolution is not achieved. The calculation of the moments in such cases is based on the maximum drug release. Furthermore, additive errors of the calculation of the area under the dissolution curve influence the values of the moments, because the integration procedure must be repeated a few times (Ferdinand and Von Hattingberg, 1984). For systems which have a complete drug release, the size of the errors depends on the number of measuring points, and also on the curve shape, which is itself an expression of the dissolution kinetics.

The parameters MDT and MRT have been used not only to describe dissolution or residence profiles with the aim to reduce the data, but also to calculate the in vitro/in vivo correlation of dissolution profiles (Brockmeier, 1986), to model the input function of the drug absorption (Voegele et al., 1988), to test the equivalence of two dissolution profiles (Brockmeier et al., 1983) or to compare different profiles statistically. All these play an important role in the pharmaceutical dosage form development, hence a statistical test method, which is based on the original data is an important feature of such comparison. Therefore, the method of calculating the statistical moments should meet the following criteria:

(1) Where calculations involve assessment of the area under the curve, the error should be minimal.

(2) The method of calculation should be applicable to various types of kinetics of the liberation process occurring.

(3) The values provided should be capable of differentiating between curves of different shape and different degree of liberation.

(4) If complete liberation is not obtained, the parameters calculated should be similar to the values which could be calculated for the complete liberation profile.

The aim of the present work was to compare different methods, which have been proposed to calculate values of the MDT and MRT in terms of the conditions given and the statistical comparison of dissolution profiles.

Modelling

There are several methods in the literature for calculating MDT or MRT. They can be divided into two main groups:

(1) Model independent methods, e.g., pragmatic plane geometry (Voegele et al., 1981; Podczeck, 1986), prospective areas (Brockmeier, 1982), transit curves (Dost, 1968).

(2) Model dependent methods, e.g., models using polyexponential equations (Von Hattingberg and Brockmeier, 1979; Wenzel, 1982), models using overlapping parabolic integration (Yeh and Kwan, 1978).

The parameters MDT and MRT are models themselves. The characterization as model independent method or model dependent method depends on the values which are used to perform the calculation. A model independent method uses the amount of the drug substance dissolved in the dissolution liquid after several known times. The model dependent methods, however, are based on different statistical functions such as polyexponential equations, which describe the dissolution profile. The calculation is undertaken from the derived function parameters.

In general, the methods are based on area calculations, which predict the error of the moments. The error will increase, if the model equation to fit the release function is less exact using model dependent methods. The calculation procedure using the overlapping parabolic integration should show maximum deviations of about 0.5% (Ferdinand and Von Hattingberg, 1984). Using the trapezoid rules, the error varies from up to 2%, dependent on the number of measuring points (Chiou, 1978).

Different drug release profiles generated by

TABLE 1

Drug release profiles for comparing different methods to calculate MDT or MRT values

Time (h)	Zero order release (%)			First order release (%)			First order release (%)		
curve	1:1	1:2	1:3	2:1	2:2	2:3	3:1	3:2	3:3
1	12.5	10.0	7.5	27.0	15.0	10.0	21.5	20.0	48.0
2	25.0	20.0	15.0	47.5	28.5	19.0	36.5	33.0	66.0
3	37.5	30.0	22.5	63.5	40.0	27.5	49.0	45.5	74.5
4	50.0	40.0	30.0	75.0	50.5	35.0	61.5	56.0	79.0
5	62.5	50.0	37.5	85.0	60.0	42.5	72.0	66.5	82.5
6	75.0	60.0	45.0	93.0	67.0	49.0	79.5	75.0	85.0
7	87.5	70.0	52.5	97.0	73.5	55.0	86.0	83.0	87.5
8	100.0	80.0	60.0	100.0	80.0	60.5	90.0	90.0	90.0
9		90.0	67.5		85.0	65.0			
10		100.0	75.0		89.0	69.5	95.5	98.0	95.0
11			82.5		93.0	73.5		100.0	
12			90.0		95.5	77.5	99.0		100.0
13			97.5 [a]		97.0	81.0	100.0		
14					98.5 [b]	84.0			
15						87.0			
16						90.0			
17						92.5			
18						94.0			
19						96.0			
20						97.0			
21						98.0			
22						99.0 [c]			

[a] 100.0% after 13 h 20 min.
[b] 100.0% after 14 h 33 min.
[c] 100.0% after 22 h 51 min.

computing will be used to compare the methods listed above. Table 1 provides the time release profiles for:

(1) Three different zero order drug release rates, which differ by a constant ratio, 1:1, 1:2 and 1:3.

(2) Three different first order drug release rates, which differ by a constant ratio, 2:1, 2:2 and 2:3.

(3) Three different first order drug release rates, which are not related to each other, but yield an equal release quantity after 8 h, 3:1, 3:2 and 3:3.

In this way, the following observations can be assessed: (a) the success of the calculation method independently of the kinetics of the drug release, (b) the ability to differentiate release profiles, and (c) the error of the MDT and MRT values calculated, if compared either with theoretical values, or the 8 h values with the values of a complete drug release curve.

A reference value for the MDT and MRT value can be determined graphically, if the complete drug release curve is available. Basically, the MRT is defined by Dost (1968) as the centre of gravity of the triangle that is equal in area to the blood level curve. The centre of gravity of the triangle is defined mathematically as the point below the intersection of the three lines, which halve the angles of the triangle. To determine the MDT of the drug release function the rate dissolution curve must be used (e.g., Fig. 1), whereas the drug residence profile is necessary to find the MRT value (e.g., Fig. 2).

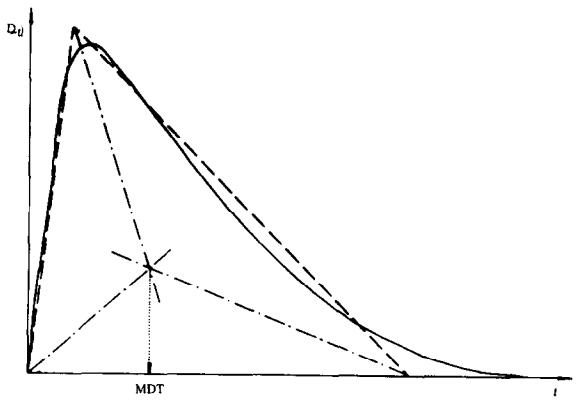

Fig. 1. Graphical determination of the mean dissolution time (MDT) using the rate dissolution curve. D_t, dissolution rate at time t.

Results and Discussion

Pragmatic plane geometry

The following simple method to determine the MDT using trapezoidal rules is often used. The

TABLE 2

Comparison of the MDT values determined by the method of pragmatic plane geometry (PPG), the method of prospective areas (PA) and the method of transit times (TF)

Curve	MDT(R)	PPG		PA		TT	
		MDT(8)	MDT(C)	MDT(8)	MDT(C)	MDT(8)	MDT(C)
1:1	4.00	4.00	4.00 [a]	2.69	2.69 [a]	5.31	5.31 [a]
1:2	5.00	4.00	5.00	2.69	3.35	5.31	6.65
1:3	6.67	4.00	6.67	2.69	4.46	5.31	8.87
2:1	1.60	2.62	2.62 [a]	3.08	3.08 [a]	4.92	4.92 [a]
2:2	2.90	3.32	4.77	2.90	5.55	5.10	8.95
2:3	4.56	3.53	7.48	2.82	8.72	5.18	14.08
3:1	1.40	2.99	3.70	2.98	5.14	5.02	7.86
3:2	1.50	3.29	3.89	2.94	4.14	5.06	6.86
3:3	1.65	1.69	2.52	3.43	5.24	4.57	6.76

MDT(R), reference value for MDT determined graphically; MDT(8), MDT calculated using the values of the first 8 h of the dissolution profile; MDT(C), MDT calculated using the complete dissolution profile.

[a] Dissolution completed after 8 h.

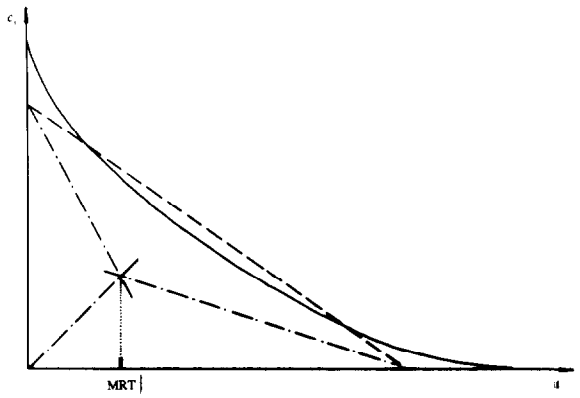

Fig. 2. Graphical determination of the mean residence time (MRT) using the residence profile of the drug substance in the dosage form. c_t, drug concentration in the dosage form at time t.

drug release profile is needed and the maximal amount of the drug substance that is dissolved (a_{tmax}) must be known. The MDT can be calculated as follows:

$$MDT = \frac{ABC}{a_{tmax}} \quad (1)$$

where ABC is the area between the drug dissolution curve and its asymptote.

Table 2 shows the results for the three sets of curves given in Table 1 using this method. The calculation is possible in all cases. The ability to differentiate the curves, however, is not possible if zero order curves, which show different release rates after 8 h, are compared by calculating the MDT based on the dissolution rates of the first 8 h only. A constant value is obtained, which is clearly incorrect. Using the complete zero order release profile, the reference MDT and the calculated value are equivalent in each case and the model provides a true representation. The 8 h MDT calculated for first order kinetics profiles differs from the MDT of the complete drug release by an average of 30%. The latter values are different from the reference MDT values by an average of 45%, if release is by a first order kinetics. The initial slope of the curve predicts the amount of the difference.

Pragmatic plane geometry can also be used to calculate the MRT value of a residence profile:

$$MRT = \frac{\int_0^t t \cdot c_t \, dt}{AUC} \quad (2)$$

The area under the residence profile curve (AUC) and the drug content in the dosage form after

TABLE 3

Comparison of the MRT values determined by the method of pragmatic plane geometry (PPG), the method of polyexponential equations (PEE) and the method of overlapping parabolic integration (OPI)

Curve	MRT(R)	PPG		PEE		OPI	
		MRT(8)	MRT(C)	MRT(8)	MRT(C)	MRT(8)	MRT(C)
1:1	1.85	2.62	2.62 [a]			2.67	2.67 [a]
1:2	2.31	3.08	3.30			3.11	3.33 [s]
1:3	3.08	3.41	4.42			3.43	4.44 [s]
2:1	1.45	2.01	2.01 [a]	2.09	2.09 [a]	2.06	2.06 [a]
2:2	2.63	2.98	3.73	4.86	3.56	3.01	3.76 [s]
2:3	4.13	3.38	5.88	8.70	5.39	3.40	5.90
3:1	2.25	2.62	2.98	3.49	2.80	2.66	3.03
3:2	2.45	2.74	2.93	3.69	2.87	2.78	3.00
3:3	2.00	2.52	3.03	4.76	3.90	2.62	3.16 [s]

MRT(R), reference value for MRT determined graphically; MRT(8), MRT calculated using the values of the first 8 h of the dissolution profile; MRT(C), MRT calculated using the complete dissolution profile.

[a] Dissolution completed after 8 h.

[s] Extrapolation based on the dissolution rates of the first 8 h satisfactory.

several times (c_t) are needed. Table 3 summarizes the results for the three sets of curves.

There is a distinctive differentiation between the curves in their dependence on the initial slope and maximal amount dissolved at 8 h for each of the kinetics. The average difference between the 8 h MRT and the MRT of the whole profiles is 30%. The difference increases, when the measurement is less complete. The deviation of the MRT values of the complete curves from the reference MRT determined graphically depends strongly on the initial slope of the curve and also has an average value of 30%.

Prospective areas

The method to determine MDT values by integrating prospective areas under curves appears to be more complicated from a mathematical point of view. According to the literature the advantage is, however, that the method is useful for incomplete release profiles (Brockmeier, 1982). The method is based on the cumulative dissolution curve. In a first step, the prospective area under the cumulative dissolution curve ($PAUC_0$) is calculated, beginning with the last measured value and recording every fractional area per time. In the second step, the fractional areas are drawn as a function of the time (f_a curve). The final part of the resulting curve is an exponential function. Therefore, any missing part of the curve, e.g., for incomplete drug release, can be calculated. In the third step, the prospective area under the f_a curve ($PAUC_1$) is determined. The MDT value results from:

$$MDT = \frac{PAUC_1}{PAUC_0} \tag{3}$$

Table 2 compares the values which were obtained using the method of prospective areas. In the case of a zero order profile the method cannot detect the difference between a complete and an incomplete release profile, if the MDT is calculated using the dissolution rates of the first 8 h only. This approach also fails to provide satisfactory answers for either of the first order models. The mean difference between the 8 h MDT values and the MDT values of the complete release curves is about 40%. The deviations between the reference values and the values of the complete release profiles are about 60%. For the second set of curves, the reference MDT reflects the time where approx. 38% of the drug substance is dissolved, whereas the MDT calculated using prospective areas appears to be the dissolution time of 62–64%.

Transit curves

Using the model of the transit curve, in a first step the estimation of the area under the drug release curve is to calculate for every fractional area per time recorded. After fitting the fractional areas against the time, the area under that, so-called 'transit curve' (AUC) must be determined. The area between the transit curve and its asymptote (ABC) is also needed. The MDT is then given by:

$$MDT = \frac{ABC}{AUC} \tag{4}$$

As shown in Table 2, the results are similar in quality to the method of prospective areas and hence this approach fails to provide a satisfactory answer.

Polyexponential equations

If the drug release process does not follow zero order behaviour, the drug residence profile can be modelled by exponential equations such as:

$$c_t = \sum_{i=1}^{n} a_i \cdot e^{b_i \cdot t} \quad i = 1(1), n \tag{5}$$

In this case, c_t is the drug amount which is still in the dosage form to the time t, and a_i and b_i are the constants of the exponential equation. The MRT can be calculated as:

$$MRT = \frac{1}{a_1} + \frac{1}{b_1} - \sum_{i=2}^{n} \left(\frac{1}{a_i} + \frac{1}{b_i} \right) \quad i = 2(1), n \tag{6}$$

The disadvantages are its inability to represent a zero order process and the fact that the exponential terms must fit the release profile exactly. Table 3 shows the results for the two first order possible curve sets. Compared to the results of the methods which use trapezoidal rules to calculate MRT values, there are unimportant differences. The similarity between the reference and calculated MRT values is not achieved in all cases. Therefore, there is no advantage in using exponential equations in terms of calculating MRT values.

Overlapping parabolic integration

The overlapping parabolic integration is also a pragmatic plane geometry method. As opposed to the trapezoid rules, however, the measuring points are connected using a parabolic function:

$$y = A + B \cdot x + C \cdot x^2 \tag{7}$$

Three measuring points are used to fit one parabolic function. The area under this function can be calculated in two steps:

$$\int_{x_1}^{x_2} = A \cdot (x_2 - x_1) + \tfrac{1}{2}B \cdot \left(x_2^2 - x_1^2\right) + \tfrac{1}{3}C \cdot \left(x_2^3 - x_1^3\right) \tag{8a}$$

$$\int_{x_2}^{x_3} = A \cdot (x_3 - x_2) + \tfrac{1}{2}B \cdot \left(x_3^2 - x_2^2\right) + \tfrac{1}{3}C \cdot \left(x_3^3 - x_2^3\right) \tag{8b}$$

Then the MRT is determined according to Eqn 2.

Because of the fact that the value of C becomes zero, if the release profile is linear, the method can be applied not only to first, but also to zero order kinetics. Table 3 summarizes the results using the method described. The parabolic function can be used to undertake an extrapolation of the MRT values of the whole release profile, if the process was not studied completely. The application was successful in four out of six cases (designated by superscript s in Table 3), and in these cases no difference between the MRT values, based on the whole release profiles extrapolated, and the MRT values calculated from the whole release profiles obtained could be detected. In general, the deviations of the calculated MRT values from the reference MRT values are an average 30%. The difference between the MRT values for the 8 h profiles and the whole release curves is less than 20%. Hence, the method of overlapping parabolic integration for calculating MRT values appears to be more suitable than the other methods tested. For most first order profiles, the MRT value calculated represents the time where the amount of the drug substance in the dosage form is reduced to about 50–55%.

Conclusions

It has thus been shown that the values of MDT and MRT can be calculated by all the methods tested, if it is required to characterize a data set by a single value. In terms of a statistical comparison, however, only those methods which are capable of differentiating between the curves independently of their order kinetics are applicable. Therefore, only the pragmatic plane geometry using the residence profile and the overlapping parabolic integration can be recommended, if the release order is unknown. Both methods calculate MRT values. The overlapping parabolic integration method provides the best estimates of MRT for first order release kinetics. The pragmatic plane geometry for calculating MDT values gives exact estimates, if a complete zero order release profile is investigated. For first order release kinetics, however, this and all other methods, which calculate MDT values, fail to estimate reference MDT values. The unreliability of these methods when assessing relatively simple drug release profiles throws doubt on their applicability to cases where drug release does not conform to a known kinetic model. Such cases represent the majority of in vitro release profiles. Hence, a universal mathematical solution is still needed. An alternative method, that can still be used, is the graphical estimation of MRT or MDT values.

References

Brockmeier, D., Bedeutung statistischer Momente der Verweildauer für die Pharmakokinetik und Biopharmazie. Dissertationsschrift, Giessen, 1982, pp. 30–31.

Brockmeier, D., Voegele, D. and Von Hattingberg, H.M., In vitro – in vivo correlation, a time scaling problem? Basic techniques for testing equivalence. *Arzneimittel-Forschung,* 33 (1983) 598–601.

Brockmeier, D., In vitro/in vivo correlation of dissolution using moments of dissolution and transit times. *Acta Pharm. Technol.,* 32 (1986) 164–174.

Chiou, W.L., Critical evaluation of the potential error in pharmacokinetics studies of using the linear trapezoidal rule method for the calculation of the area under the plasma level-time curve. *J. Pharmacokinet. Biopharm.,* 6 (1978), 539–546.

Dost, F.H., *Grundlagen der Pharmakokinetik,* Georg Thieme Verlag, Stuttgart, 1968.

Ferdinand, W. and Von Hattingberg, H.M., Fehlerfortpflanzung bei der Berechnung von Momenten. *Methods Findings Exp. Clin. Pharmacol.,* 6 (1984) 605–608.

Hays, W.L., *Statistics for the Social Sciences,* 2nd Edn, Holt, Rinehart & Winston, London, 1973, pp. 215–248.

Podczeck, F., Beiträge zum Einsatz mathematischer Methoden zur Entwicklung fester peroraler Arzneiformen. Dissertationsschrift, Halle/Saale, 1986, p. 49.

Voegele, D., Von Hattingberg, H.M. and Brockmeier, D., Ein einfaches Verfahren zur Ermittlung von in vitro-/in vivo Zusammenhängen in der Galenik. *Acta Pharm. Technol.,* 27 (1981) 115–120.

Voegele, D., Brockmeier, D. and Von Hattingberg, H.M., Modelling of input function to drug absorption by moments. *Proceedings of the Symposium on Compartmental and Noncompartmental Modelling in Pharmacokinetics,* Smolenice, Czechoslovakia, 12–16 Sept. 1988, pp. 1–14.

Von Hattingberg, H.M. and Brockmeier, D., Standardisierung von Rechenmodellen zur Prüfung der Bioverfügbarkeit. In Rietbrock, N. and Schnieders, B. (Eds), *Bioverfügbarkeit von Arzneimitteln,* Gustav Fischer Verlag, Stuttgart, 1979, p. 191.

Wenzel, U., Beiträge zur Entwicklung einer peroralen Retard-Arzneiform und zur Physik der Tablettierung. Dissertationsschrift B, Halle/Saale, 1982, p. 26.

Yeh, K.C. and Kwan, K.C., A comparison of numerical integrating algorithms by trapezoidal, Lagrange and spline approximation. *J. Pharmacokinet. Biopharm.,* 6 (1978), 79–96.

Wagner, J.G., Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules. *J. Pharm. Sci.,* 58 (1969), 1253–1257.