Acta Poloniae Pharmaceutica – Drug Research, Vol. 69 No. 1 pp. 81–85, 2012 ISSN 0001-6837
Polish Pharmaceutical Society

PHARMACEUTICAL TECHNOLOGY

APPLICATION OF THE PIECEWISE RATIONAL QUADRATIC INTERPOLANT TO THE AUC CALCULATION IN THE BIOAVAILABILITY STUDY

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Abstract: This study presents an application of the piecewise rational quadratic interpolant to the AUC calculation in the bioavailability study. The objective of this work is to find an area under the plasma concentration-time curve (AUC) for multiple doses of salbutamol sulfate sustained release tablets (Ventolin® oral tablets SR 8 mg, GSK, Pakistan) in the group of 24 healthy adults by using computational mathematics techniques. Following the administration of 4 doses of Ventolin® tablets 12 hourly to 24 healthy human subjects and bioanalysis of obtained plasma samples, plasma drug concentration-time profile was constructed. The approximated AUC was computed by using computational mathematics techniques such as extended rectangular, extended trapezium and extended Simpson's rule and compared with exact value of AUC calculated by using software – Kinetica® to find best computational mathematics method that gives AUC values closest to exact. The exact values of AUC for four consecutive doses of Ventolin® oral tablets were 150.58, 157.81, 164.41 and 162.78 ng×h/mL while the closest approximated AUC values were 149.24, 157.33, 164.25 and 162.28 ng×h/mL, respectively, as found by extended rectangular rule. The errors in the approximated values of AUC were negligible. It is concluded that all computational tools approximated values of AUC accurately but the extended rectangular rule gives slightly better approximated values of AUC as compared to extended trapezium and extended Simpson's rules.

Keywords: salbutamol sulfate, area under curve (AUC), extended rectangular rule, extended trapezium rule, extended Simpson's rule

The terms "pharmacokinetics" represents drug absorption, distribution, metabolism and excretion in the body. Plasma and urine are major biofluids used for the calculation of pharmacokinetics. However, the former is considered a good source of informations. Plasma drug concentration-time profile is used for the calculation of various pharmacokinetics parameters such as area under the curve (AUC), drug absorption constant (K_a), drug elimination constant (K), volume of distribution (V_d) and others. AUC, an important pharmacokinetic parameter, provides basic informations regarding drug transit time in body because it is proportional to the amount of drug absorbed and can be calculated by many techniques. Statistically, there are many approaches such as extended rectangular rule, extended trapezium rule and extended Simpson's rule, which can be employed to evaluate AUC from plasma drug concentration-time data (1–3).

Recent work is an application of the piecewise rational quadratic interpolant to the AUC calculation in the bioavailability studies as piecewise monotonic interpolant is easily constructed and numerical experiments show that the method produces good quality curves. As the drug concentration data were taken at some points separated by unequal intervals, not at all, thus non-uniform data were obtained and it was needed to convert them into equally spaced data. For this, monotonic piecewise rational quadratic interpolant was used. Different numerical methods are applicable for finding AUC such as extended rectangular rule, extended trapezium rule and extended Simpson's rule (2, 4). The extended rectangular rule is very simple and interesting math-

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ematical method that provides the elegant solution. It is used after dividing the area under the curve into a large number of rectangles. The accuracy of approximate solution can be increased (decreased) by increasing (decreasing) the step size (3). The extended trapezium rule is another method that is used to estimate AUC in the given limits. However, the trapezium rule is used to find AUC using two points for each application. The area under the plasma drug concentration-time curve is divided into several trapeziums. Each interval has length "h". The extended trapezium rule is also applied. The quadratic polynomials were used to approximate the integral of a function by extended Simpson's rules (4–7). The extended Simpson's rule can be derived by integrating a second order Lagrange polynomial interpolating the function at three equally spaced points. The extended Simpson's method is used to compute AUC in the given limits by dividing the area into a number of curvilinear trapeziums. The number of trapeziums is even (5).

This study compares three methods (extended rectangular rule, extended trapezium rule and extended Simpson's rule) for AUC evaluation in pharmacokinetic studies in human for 4 consecutive doses of an anti-asthmatic drug, salbutamol sulfate sustained release tablets (Ventolin® oral tablets SR 8 mg, GSK, Pakistan) and to find the comparison of exact and approximate values of AUC. For approximate solution, the previously generated experimental data of drug concentration-time profile for multiple oral-doses were used. These data were approximated by using rational quadratic interpolant. The approximation was compared to exact AUC by using a computer program written in FORTRAN 95.0.

EXPERIMENTAL

Bioavailability study

his work is based on the bioavailability study of Ventolin® oral tablets carried out in 24 healthy male young non-smoker human subjects (61–85 kg mean body weight) with no clinical and biochemical abnormality. Following the administration of 4 doses of Ventolin® oral tablets 12 hourly to 24 healthy human in a crossover study and bioanalysis of obtained plasma samples using validated HPLC method (8), plasma drug concentration-time profile was constructed for each subject. The mean plasma drug concentration *versus* time curve is presented in Figure 1. From the plasma drug concentration *versus* time profiles, exact values of various pharmacokinetic parameters such as AUC were calculated for individual subjects using software "Kinetica®" based on non-compartment model approach and thus the results obtained were considered as reference (exact results). This study was approved (Registration No. 18-Pharm/IUB-2008) by the Board of Advance Studies and Research, the Islamia University of Bahawalpur, Pakistan. It was conducted in accordance with the Good Clinical Practice and Helsinki declaration of human use in *in vivo* studies.

Numerical methods used

Extended rectangular rule, extended trapezoidal rule and extended Simpson's rule were used for finding approximated AUC. The range of inte-

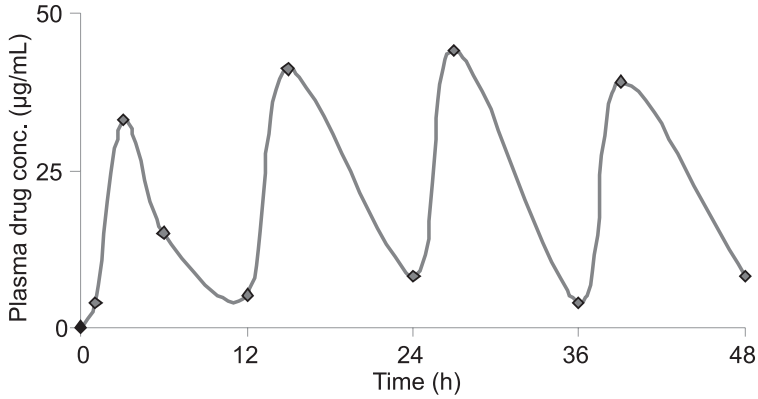

Figure 1. Plasma drug concentration *vs.* time profiles after 4 consecutive doses to 24 healthy human subjects (if one interpolant was used for the whole time interval)

Table 1. Exact mean values of pharmacokinetic parameters for four doses of Ventolin® tablets 12 hourly and approximate values of AUC when interval is 0.00001, 0.0001 and 0.001.

Exact values of AUC (ng.h/mL)		No. of doses			
		First dose 150.58	Second dose 157.81	Third dose 164.41	Fourth dose 162.78
Approximate values of AUC (ng.h/mL)					
Approximate AUC values when interval = 0.00001	extended rectangular rule	149.245962	157.336171	164.25857	162.289224
	extended trapezium rule	149.244423	157.334269	164.25649	162.287349
	extended Simpson's rule	149.244429	157.334274	164.25650	162.287341
Approximate AUC values when interval = 0.0001	extended rectangular rule	149.136645	157.228273	164.15197	162.181982
	extended trapezium rule	149.136492	157.228083	164.15177	162.181794
	extended Simpson's rule	149.136389	157.227956	164.15163	162.181668
Approximate AUC values when interval = 0.001	extended rectangular rule	149.131635	157.222660	164.14615	162.176157
	extended trapezium rule	149.131148	157.222641	164.14613	162.176138
	extended Simpson's rule	149.131138	157.222629	164.14611	162.176126

Table 2. Comparison of exact and approximate values of area under plasma concentration time curve using extended rectangular rule, extended trapezium rule and extended Simpson's rule when interval is 0.00001.

		No. of doses			
		First Dose	Second dose	Third dose	Fourth dose
	Exact area	150.581947	157.813172	164.417823	162.787969
Extended rectangular rule	Approximate area	149.245962	157.336171	164.258577	162.289224
	Error	1.335986	0.477005	0.159246	0.498745
	Percentage error	0.887%	0.302%	0.097%	0.306%
Extended trapezium rule	Approximate area	149.244423	157.334269	164.256495	162.287349
	Error	1.337524	0.478907	0.161328	0.500619
	Percentage error	0.888%	0.303%	0.098%	0.308%
Extended Simpson's rule	Approximate area	149.244429	157.334274	164.256500	162.287341
	Error	1.337519	0.478902	0.161323	0.500628
	Percentage error	0.888%	0.303%	0.098%	0.308%

gration [first time point (t_0), last time point (t_k)] was divided into N subintervals for different values of natural number – N. The points of division are:

$$x_0 = t_0,\ x_1,\ \ldots..x_N = t_k$$

$$\int_{x_0=t_0}^{x_N=t_k} C(t)dt = [AUC]_{x_o}^{x_N} = [AUC]_{x_o}^{x_1} + [AUC]_{x_1}^{x_2} + \cdots\cdots\cdots + [AUC]_{x_{N-1}}^{x_N} \quad \text{(Eq.1)}$$

If only two time values x_i, x_{i+1} are taken then trapezoidal rule is:

$$[AUC]_{x_i}^{x_{i+1}} = \frac{(x_{i+1} - x_i)}{2}[C(x_i) + C(x_{i+1})] \quad \text{(Eq. 2)}$$

If extended trapezium rule is applied for finding approximated AUC, we get:

$$[AUC]_{x_o}^{x_N} = \frac{h}{2}\left[C(x_o) + 2\sum_{i=1}^{N-1} C(x_i) + C(x_N)\right] \quad \text{(Eq. 3)}$$

where, $h = \frac{(x_N - x_o)}{N}$

If extended Simpson's rule is applied for finding approximated AUC, then we get:

$$[AUC]_{x_0}^{x_N} = \frac{h}{3}\left[C(x_0) + C(x_N) + 4\sum_{i=1}^{N/2} C(x_{2i-1}) + 2\sum_{i=1}^{N/2-1} C(x_{2i})\right] \quad \text{(Eq. 4)}$$

When extended rectangular formula is applied for calculating approximated AUC then we get:

$$[AUC]_{x_o}^{x_N} = h\sum_{i=1}^{N-1} C(x_i) \quad \text{(Eq. 5)}$$

The analytic values of can be calculated mathematically. A monotonic piecewise rational quadratic interpolant s(t) was applied to approximate the value of concentration between the given concentration *versus* time data points. Then, approximated concentration values were obtained at additional values of time by the values of s(t). The s(t) was calculated as follows (9, 11):

Let $C_i = C(t_i), C_{i+1} = C(t_{i+1})$, $d_i = C'(t_i)$ *and* $d_{i+1} = C'(t_{i+1})$

Let, $h_i = t_{i+1} - t_i$, for i = 0, 1, 2, ..., k – 1

$\theta = (t - t_i)/h_i$ for $t \in [t_i, t_{i+1}]$

$\Delta_i = (C_{i+1} - C_i)/h_i$

$$s(t) = \begin{bmatrix} p_i(\theta)/Q_i(\theta) & if \Delta_i \neq 0 \\ C_i & if \Delta_i = 0 \end{bmatrix} \quad \text{(Eq. 6)}$$

where

$P_i(\theta) = \Delta_i C_{i+1}\theta^2 + (C_i d_{i+1} + C_{i+1} d_i)\theta(1-\theta) + \Delta_i C_i(1-\theta)^2$

$Q_i(\theta) = \Delta_i\theta^2 + (d_{i+1} + d_i)\theta(1-\theta) + \Delta_i(1-\theta)^2$

The derivatives d_i and d_{i+1} can be approximated from experimental data (10). The central differences approximation to C'(t) that is commonly used in numerical analysis, is given by (11):

$$C'(t_i) = \frac{C(t_i + h) - C(t_i - h)}{2h} \quad \text{(Eq. 7)}$$

where, h = constant. In this study, the spacing of the concentration data is not uniform and the central difference approximation to C'(t) was calculated by using equation '(2)' and defined by (11):

$$d_i = C'(t_i) \approx \frac{C(t_i + h_i) - C(t_i - h_{i-1})}{h_i + h_{i-1}}, \; i = 1,2,.....k-1 \quad \text{(Eq. 8)}$$

It is closer to the exact values of derivatives as compared to the values of the derivatives calculated by using forward or backward difference. So $C'(t_k)$ and $C'(t_0)$ that are initial and final values of derivatives can be found using forward and backward differences such as (11):

$$C'(t_0) \approx \frac{C_1 - C_0}{h_0} \quad \text{(Eq. 9)}$$

and

$$C'(t_k) \approx \frac{C(t_k) - C(t_k - h_{k-1})}{h_{k-1}} \quad \text{(Eq. 10)}$$

These are backward and forward difference approximations. The approximate value of C(t) was calculated by using the rational quadratic interpolant. The data were generated by the approximation of s(t) at very small intervals like 0.00001. For multiple dosing data, the quadratic rational interpolant s(t) gave the approximate values at every point. The above data were used to draw curve for each dose and the area under each curve was determined. For this, different numerical methods were employed such as extended rectangular rule, extended trapezoidal rule and extended Simpson's rule. The computer program of these numerical methods (Microsoft Power Station FORTRAN) was produced to calculate AUC using the approximate values of s(t).

RESULTS AND DISCUSSION

The exact mean values of pharmacokinetic parameters such as AUC, were calculated from plasma drug concentration *versus* time profiles by using software "Kinetica®" and are shown in Table 1 and then calculated the approximate values of AUC. For this purpose we used data which were obtained for Ventolin® tablets.

The rational quadratic interpolant s(t) was used for calculating the approximate values of plasma drug concentration at each point. A computer program for rational quadratic interpolant was produced to calculate the values of drug concentration at each point. The approximated concentration values at additional points using s(t) taking step sizes 0.001, 0.0001 and 0.00001 were generated to find AUC by using different numerical methods such as extended rectangular methods, extended trapezium method and extended Simpson's method.

The exact and approximate values of AUC were compared to check the difference. It was observed that there was a negligible difference between the exact and approximate values of AUC as calculated by above mentioned numerical rules. Approximate values of AUC for given data by extended rectangular, extended trapezium and extended Simpson's rules, respectively, are presented in Table 1, when length of step size (h) is 0.001, 0.0001 and 0.00001 by using all of three rules. For step size 0.00001, there was the best approximation

of AUC and the result shows that an increase in the number of trapezium gives more accuracy.

Table 2 shows that approximate AUC in all cases is slightly less than the respective exact AUC. However, the approximate values of AUC are close to the respective exact values of AUC for each given length of interval. The difference between the approximate values of AUC may be significant from mathematical point of view but the difference is negligible from practical point of view.

It was also noted that with decreasing the value of length of subintervals, the approximate values of AUC became closer to the respective exact values. Moreover, the approximate value of AUC computed by extended rectangular rule is closest to the exact values of AUC. This is because of a shape of plasma concentration-time curve. Table 2 shows the maximum value of error percentage that is at the most one and at least 0.097%. It verifies that the approach adopted is very successful and the approximate values of AUC are almost the same as exact from the practical point of view. An advantage of this approach is that there is no need to calculate other pharmacokinetic parameters for the calculation of AUC.

CONCLUSION

All computational tools approximated values of AUC accurately but among three computational mathematics techniques such as extended rectangular rule, extended trapezium and extended Simpson's rule, extended rectangular rule gives slightly better but non-significantly different results regarding approximation of AUC as compared to other approximation methods.

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Received: 12. 07. 2010