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STOCHASTIC PRINCIPLES AND MATHEMATICAL ANALYSIS USEFUL IN DISSOLUTION TESTING OF A SOLID DOSAGE FORM

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ABSTRACT

The dissolution rate of individual tablets within a lot is considered to be of a random nature. The connection between classical statistics and the stochastic approach, together with their dependence, is presented. By formulating the hypothesis specific to the basic question of interest, a methodology for determining the required number of solid dosage form for the dissolution rate assessment of a lot is suggested.

INTRODUCTION

Differences in dissolution rate have usually been found among solid dosage forms from different manufacturers, among different lots from the same manufacturer and sometimes even within the same lot. The determination of the dissolution rate of a lot of a tablet, for example, is usually carried out on a

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certain number of tablets and the results are used to assess the overall dissolution rate of the lot as a whole. The reliability of such an assessment depends on the number of tablets involved in the test. Hence, a special formula, one that is directed at the determination of the number of the dosage form involved in the analysis, becomes of interest. It should be mentioned that in most arbitrary protocols, the usual statistical methods of analysis are correct, but a suitable criterion is needed to determine the required number of a solid dosage form for the analysis. The object of the present paper is to formulate a procedure that may serve as a basis for determining the reliability of testing the dissolution rate of a lot of a solid dosage form by measurement on a limited selection from that lot.

THEORETICAL

The dissolution rate is a function of a certain number of parameters which may vary in the process of preparing a tablet (1). Although it is impossible to take into account all the factors exerting an influence on the *in vivo* or *in vitro* dissolution rate of a tablet, but it can be assumed that the variation of the parameters is of a random nature and the distribution of the dissolution rate estimates of individual tablets within a lot is in accordance with the normal distribution law (2). Moreover, it can be assumed that there are no systematic errors in the measurements. Then the difference between the result of an *in vitro* measurement of dissolution rate, V, and the *in vivo*

value, υ, will equal the random error of E=V-υ. Based on the theory of a normal law of distribution of random error, the probability density of the random error, $f_1(E)$, may be written in the following form (3):

$$f_1(E) = \frac{1}{\sigma_E\sqrt{2\pi}} \exp\left(-\frac{E^2}{2\sigma_E^2}\right) \qquad (1)$$

where σ_E^2 is the variance of the random error. The probability density of the in vivo dissolution rate of the tablets, $f_2(\upsilon)$, by virtue of the above assumption of a normal distribution within a lot, can be written in the following form:

$$f_2(\upsilon) = \frac{1}{\sigma_\upsilon\sqrt{2\pi}} \exp\left\{-\frac{(\upsilon-\mu)^2}{2\sigma_\upsilon^2}\right\} \qquad (2)$$

where μ is the mean of rates of dissolution of the lot, it is a real constant and can be considered as mathematical expectancy. The variance of σ_υ^2 of the <u>in vivo</u> dissolution rates is a positive constant. The equation gives the familiar bell-shaped curve so often associated with statistics. The density, $f_2(\upsilon)$, is largest at $\upsilon = \mu$, and if σ is small, most of the area under the density is concentrated near μ. Since υ (<u>in vivo</u> dissolution rate) and E (the random error) are mutually independent random quantities, the expression

$$f(\upsilon, E) = f_1(E)f_2(\upsilon)$$

is valid for their combined probability density. The probability density of the quantity V, the <u>in vivo</u> dissolution rate, can be determined from the following equality

$$f(V) = \int_{-\infty}^{+\infty} f_2(\upsilon)\ f_1(V-\upsilon)\ d\upsilon \qquad (3)$$

By substituting equations 1 and 2 in 3 one can obtain the following relationship.

$$f(V) = \int_{-\infty}^{+\infty} \frac{1}{\sigma_\upsilon \sigma_E 2\pi} \exp\ \{-[\ \frac{(\upsilon-\mu)^2}{2\sigma_\upsilon^2} + \frac{(V-\upsilon)^2}{2\sigma_E^2}]\}\ dx \qquad (4)$$

If we define the variance of the <u>in vivo</u> rates in the following manner

$$\sigma_V^2 = \sigma_\upsilon^2 + \sigma_E^2$$

and designate

$$\bar{\mu} = \frac{\mu\sigma_E^2 + V\sigma_\upsilon^2}{\sigma_V^2}$$

and $$\bar{\sigma}^2 = \frac{\sigma_\upsilon^2\ \sigma_E^2}{\sigma_V^2}$$

then equation 4 will have the following form

$$f(V) = \int_{-\infty}^{+\infty} \frac{1}{\sigma_\upsilon \sigma_E 2\pi} \exp\ \{\frac{(V-\mu)^2}{2\sigma_V^2}\}\ \exp\ \{-\frac{(\bar{\upsilon}-\bar{\mu})}{2\bar{\sigma}^2}\} \qquad (5)$$

On taking υ out of the integral, and evaluating the integral of <u>in vitro</u> probability density function we obtain

$$f(V) = \frac{1}{\sigma_V\sqrt{2\pi}} \exp\ \{-\frac{(V-\mu)^2}{2\sigma_V^2}\} \qquad (6)$$

Thus the dissolution rate is a random quantity characterized by a normal distribution function with a mathematical expectancy μ and with a variance σ_V^2, wherein

$$\sigma_V^2 = \sigma_\upsilon^2 + \sigma_E^2$$

EXPERIMENTAL

Suppose that from a lot of a tablet a selection is made, m times of an assigned number n, to which by means of a stirred-vessel type apparatus, for example, are assigned dissolution rate of $V_{i\mathring{J}}$ ($i = 1,2,\ldots,n$; $\mathring{J} = 1,2,\ldots,m$). The distribution function of the individual tablet within the lot can be represented on the scale of σ_V, *i.e.*, the ratio

$$V_{i\mathring{J}} = \frac{V-\mu}{\sigma_V} \tag{7}$$

can be adopted as a random value of the measured *in vitro* dissolution rate. Then the probability density of the measure dissolution rate $V_{i\mathring{J}}$ will be described by a function of the form of Eq. 6 with $\mu = 0$ and $\sigma_V = 1$. The mean of dissolution rates of n tablet in each of the m measurements, $\bar{V}_{\mathring{J}}$, can be calculated from the equation

$$\bar{V}_{\mathring{J}} = \frac{1}{n} \sum_{\mathring{J}=1}^{m} V_{i\mathring{J}} \tag{8}$$

The mean of dissolution rate of all measurements (*i.e.* nm) and related standard deviation, SD, can be determined from the following relationships:

$$\bar{\bar{V}} = \frac{1}{m} \sum_{\mathring{J}=1}^{m} \bar{V}_{\mathring{J}} \tag{9}$$

and

$$SD = \sqrt{\frac{1}{m-1} \sum_{\mathring{J}=1}^{m} (\bar{V}-\bar{\bar{V}})^2} \tag{10}$$

Note that $\bar{V}_{\overset{\circ}{J}}$ and SD can be obtained on the scale of σ_V, so that

$$\bar{V}_{\overset{\circ}{J}} = \frac{\bar{V}-\mu}{\sigma_V} \tag{11}$$

$$\text{and SD} = \frac{Sn}{\sigma_V} \tag{12}$$

where $\bar{V}n$ = The mean of the <u>in vitro</u> dissolution rates for the measurement of n tablets.

Sn = The empirical standard deviation for the measurement of n tablets.

Since in measurements on a limited selection of tablets any $\bar{V}_n$ value may occur as an estimate of the mean μ, it is necessary to indicate the range, C, of the deviation of $\bar{V}_n$ from μ. Moreover, the probability P that the normal distribution of the random quantity $\bar{V}_n$ will take on a value in the range from $\mu + C$ is derived by means of the following probability integral:

$$P = \frac{2}{S_n\sqrt{2\pi}} \int_o^{\mu+C} e^{-\frac{(\bar{V}n-\mu)^2}{2S_n^2}} d\bar{V}n \tag{13}$$

Substituting the following symbols in Eq. 13,

$$M = \frac{\bar{V}n-\mu}{Sn} = \frac{\bar{V}_{\overset{\circ}{J}}}{SD}$$

$$d = \frac{C}{\sigma_V} \text{ and } C' = \frac{C}{\sigma_V}$$

$$\therefore d = \frac{C'}{SD}$$

we reduce it to the tabulated probability integral (4,5)

$$P = \phi\ (d) = \sqrt{\frac{2}{\pi}} \int_0^d e - \frac{M^2}{2}\, dt \qquad (14)$$

where d is the range of the deviations on the σ_V scale. The function d (P), the inverse of the probability integral 14, can also be tabulated and enables the value of C or C' to be found with an assigned probability P:

$$C = d(P)\ \sigma_V,\ C' = d(P)\ SD \qquad (15)$$

DISCUSSION

For a given solid dosage form, a graph of empirical standard deviation plotted against n has the curve characteristic of an inverse proportion, that can be generated in the course of an experiment. By using the dependence of standard deviation on n and Eq. 15, it is possible with a probability P to determine C' as a function of the number of tablets selected for a dissolution test. The relationship between C', n and P (*i.e.*, the dependence of the confidence interval C' on the number n of tested tablets, for different probability values) can also be tabulated or presented as a family of curves. Therefore, for a desired P and a given confidence range C', it is possible to determine the minimum number of tablets necessary for the dissolution testing. Let us carry out a hypothetical evaluation.

Suppose that from the relationship between n, C' and P, that can be simulated as a family of curves, the values of C' for n = 6 and n = 15 for some given value of P are determined. Then with

σ_V being known from the generated curve of the empirical standard deviation versus n and Eq. 12, the confidence interval $C = C'\sigma_V$ can be determined. Let us assume that with a P = 0.95 of 6 tablets C = 0.28, and with n = 15 and the same P value C = 0.21. This means that with a reliability value of 95%, the value of the mean of the dissolution rate of the lot, μ, may differ from the measured value by not more than 28% if 6 tablets are tested, or by not more than 21% if fifteen tablets are tested. Obviously for a desired confidence interval of C = 0.1 at P = 0.95 one has to select a different n value that is greater than 15.

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