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Some comments on a method to quantify modified drug release

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Nimmerfall and Rosenthaler (1986) provide a way to quantify modified release of drugs. Their modification of the method of area deviation according to Boxenbaum (1984) is based on the calculation of the ideal plasma concentration ($c_{p_{ideal}}$), which is the average plasma concentration during time interval t_r. The absolute retard effect $R_{i_{abs}}$ is defined as

$$R_{i_{abs}}(\%) = 100\left(1 - \frac{AUC_{Di}}{AUC_{exp}}\right)$$

in which AUC_{Di} is the positive area deviation of the ideal plasma concentration, while AUC_{exp} represents the experimental AUC.

This method has been claimed to yield a number of advantages over other modified drug release quantifying methods. It is relatively insensitive to so called drug bursts, but on the other hand it does characterize the shape of the plasma concentration/time curve, whereas statistical moment analysis does not.

The authors propose the following arbitrary criterion for a modified drug release formulation to be acceptable:

$R_{i_{abs}} \geq 75\%$

using either *t*-statistics for testing significance or the more rapid 75/75 decision rule (75% or more of the samples giving $R_{i_{abs}} \geq 75\%$).

From our collection of dapsone (DDS) plasma concentration/time curves, as obtained after administration of a DDS depot injection to leprosy patients, some less favourably shaped curves were selected. These were characterized by a too low DDS concentration at the end of the study period (28 days, the intended dosage interval), while on the other hand unnecessarily high DDS peak concentrations are measured (Fig. 1). Nevertheless

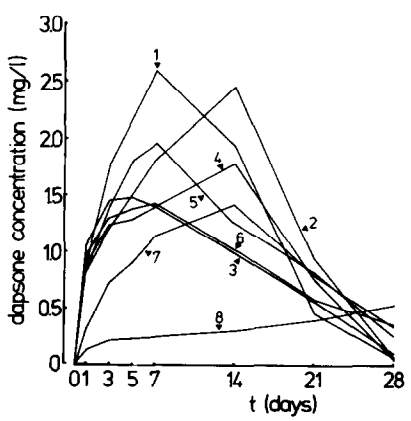

Fig. 1. Dapsone serum concentration/time curves after administration of a dapsone depot injection to leprosy patients. Nos 1–8 represent curves with $R_{i_{abs}}$ values increasing from 70.9 to 85.8%.

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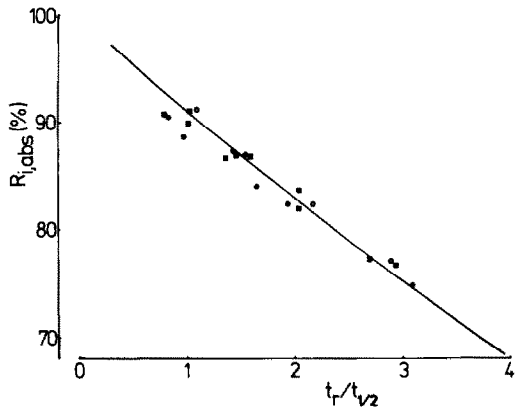

Fig. 2. Relation between $t_r/t_{1/2}$ and $R_{i_{abs}}$. Solid line theoretical relation after i.v. bolus injection; ■, experimental results after i.v. administration of dapsone to healthy volunteers; ○, experimental results after oral administration of dapsone to healthy volunteers.

only one curve yields a $R_{i_{abs}}$ value below 75% (no. 1, 70.9%). The other curves result in $R_{i_{abs}}$ values increasing from 77.5 for no. 2 to 85.8% for no. 8 (mean ± S.D.: 80.8 ± 2.9%), suggesting, that the proposed criterion might be too easy to fulfil.

Even more striking are the results obtained if the method is applied to a hypothetical plasma concentration/time curve after i.v. administration of a bolus injection of a drug, which shows perfect first order elimination pharmacokinetics, without a distribution phase. In Fig. 2 the calculated $R_{i_{abs}}$ values of such a curve are presented as a function of the time interval (expressed as the number of elimination half lives $t_{1/2}$). As long as $R_{i_{abs}} \leq 3 \times t_{1/2}$ the results will fulfil the requirements, although one can hardly call an i.v. injection a sustained release formulation.

The method was also tested to a number of curves obtained after oral and i.v. administration of DDS to healthy volunteers. The calculated $R_{i_{abs}}$ values of both routes of administration corresponded very well with the theoretical curve as presented in Fig. 2. After oral administration $R_{i_{abs}}$ varied from 86.7 to 91.2% ($n = 5$; $t_{1/2}$ varying from 15.6 to 29.2 h), if $t_r = 24$ h. With $t_r = 48$ h values ranged from 74.7 to 84.0% ($n = 5$). After i.v. administration these values were 86.6–90.8% and 76.6–86.8% ($n = 5$; $t_{1/2}$ ranging from 16.4 to 30.4 h), for $t_r = 24$ h and 48 h, respectively. A good correlation ($r > 0.82$, $P < 0.05$) existed between $R_{i_{abs}}$ and $t_{1/2}$, which indicates the dependence of $R_{i_{abs}}$, not on the elimination rate of the drug, but on t_r.

Special attention should be given to curve no 8 in Fig. 1. The DDS concentration steadily increases until 28 days after injection. This indicates excellent sustained release, although $R_{i_{abs}}$ is only 85.8%. The method by Nimmerfall and Rosenthaler does not seem to be fit here either. In this case t_r is chosen too short.

One can foresee, that if $R_{i_{abs}}$ is calculated from steady-state plasma concentration/time curves instead of curves obtained after single administration even better values of $R_{i_{abs}}$ will result. As yet the method does not seem to be fit for use in steady state. Unfortunately this restricts its applicability considerably.

The following is recommended: the dosage interval required for the drug formulation to be tested should be taken as t_r. This interval should not be shorter than 3 times the elimination half life. $R_{i_{abs}}$ (t_r) should then be calculated from the plasma concentration/time curve obtained after single administration and with the initial drug concentration being 0. Acceptable modified drug release must be defined as giving an $R_{i_{abs}} \geq 85\%$.

If these suggestions are taken into consideration the method by Nimmerfall and Rosenthaler provides a simple and reliable means to quantify modified drug release.

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