that might influence the wavelength distribution of the reflected light (Nokhodchi and Javadzadeh 2007). The presence of water molecules can also change the polarity of the microenvironment which may leads to solvatochromism (Gordon and Gregory 1987). Adsorbed water can further influence the reactant conformation, intra- and intermolecular hydrogen bonding properties or facilitate hydrogen atom abstraction. All these parameters are important for photochromism (i.e. reversible color change upon exposure to light) (Nokhodchi and Javadzadeh 2007). The sample surface temperatures will, however, increase during exposure and this can lead to evaporation of the moisture on the sample surface (Tønnesen and Baertschi 2004). Moisture can be re-adsorbed from the atmosphere when the samples are cooled in an open container. This might explain the large fluctuations in the total color change as a function of lag-time. In the case of RF the lag-time will have a large impact on whether the sample should pass the test or be discarded. A color tolerance limit of ΔE^*ab in the range 1.5–2 would be reasonable for many pharmaceutical preparations (Tønnesen et al. 2007). According to this criterion the samples would only pass the photostability test (i.e. total exposure 22045 kJ/m^2) in cases where the color evaluation was made at a certain lag-time after exposure, assumed that the samples are stored under ambient conditions in the dark.

To our knowledge this aspect of the photostability testing protocol has not previously been addressed. Our results may possibly be valid for many photolabile, (slightly) hygroscopic substances and emphasize the need for a standardization of the lag-time between exposure and analysis in order to achieve maximum reproducibility and representative results.

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Influence of pre-systemic modifications on the drug performance

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Received March 10, 2008; accepted March 17, 2008

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Pharmazie 63: 546–548 (2008)
doi: 10.1691/ph.2008.8068

Influences of technological and other pre-systemic modifications on the drug performance play a pivotal role in drug development and optimization. The paper evaluates these influences within a framework of the sensitivity theory. Deviations of the drug performance that were caused by modified pre-systemic parameters are predicted and compared with those obtained *in vivo*. A close correspondence between them demonstrates feasibility of the approach presented and its usability as an alternative or suplementary means of the *in vitro-in vivo* correlation analysis.

Novel principles and technologies used in drug manufacturing and optimisation call for effective means that could analyse influences of pre-systemic modifications on a given performance measure, e.g. the concentration-time profile, area under the concentration curve etc. In the approach presented here the direct influences of modified pre-systemic parameters on the concentration profile are expressed and predicted explicitly. Both the magnitudes and directions of the influences are displayed though continuous functions of time rather then by a single value. The approach is applicable regardless of the dosage forms and relating kinetics (linear-nonlinear). It is also discriminating enough, able to assess influences of virtually all technological and/or pre-systemic processes, like disintegration, dissolution and absorption. This means a significant enrichment of the knowledge the designer has on her/his disposal when designing a new or modifying an already manufactured dosage form. Explicitly expressed sensitivities of the concentration profile to any modifications of pre-systemic parameters allow singling out their influences. Besides, the sensitivities provide valuable information about the "degree of belief" to which the *in vitro* dissolution test may be considered as a waiver of bioequivalence studies.

It is worth mentioning that sometimes an opinion appears, advocating the possibility *to predict* the fate of a drug in the body by pharmacokinetic modeling. A problem is that such a model can predict nothing at all, but reflects a specific real process the model is tuned to. Hence, it lacks generalization abilities. In fact the actual behaviour of a

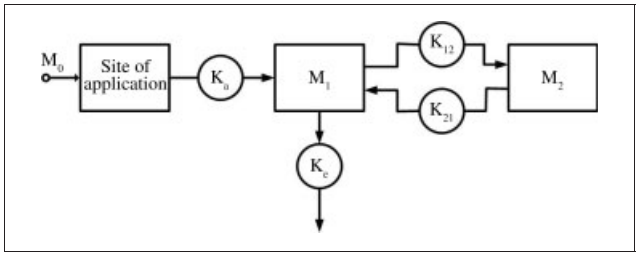

Fig. 1: Two-compartment model of e.v. application where M_0 is an administered dose, M_1 is an instantaneous drug amount in the central compartment, M_2 is an instantaneous drug amount in the peripheral compartment, k_a is an absorption rate constant, k_{12}, k_{21} are hybrid rate constants, k_e is an elimination rate constant

drug in a body may be strongly sensitive to manufacturing processes, post-aproval modifications and other changes of pre-systemic processes. Therefore the designer needs to know not only a nominal behaviour of a drug in the body but also its tendency to deviate from the nominal. Both the directions and quantities of deviations induced by the modified pre-systemic parameters can be easily predicted by the sensitivity analysis (Rosenwasser and Yusupov 2000). If even a small technological modification engender significant deviation of the concentration profile in comparison with that of predicted, then the dissolution test cannot surrogate bioequivalence studies. Let us suppose a general form of an n-compartment pharmacokinetic model (Wagner 1975)

$$\frac{dM_i(t)}{dt} = F_i(M_1, M_2, \ldots, M_n, q_1, q_2, \ldots, q_m) \qquad (1)$$

where
F_i $i = 1, 2, \ldots n$ is a (possibly nonlinear) function related to the i-th compartment
$M_i(t)$ is a drug amount in the i-th compartment at time "t'
q_j, $j = 1, 2, \ldots m$ is the j-th parameter
n is a number of compartments
m is a number of model parameters

The sensitivity of the amount M_i to the deviation ∂q_j of the parameter q_j is defined as a partial derivation of M_i w.r.t parameter q_j, i.e.

$$S_{M_i,q_j} = \frac{\partial M_i(t)}{\partial q_j} \qquad (2)$$

The definition indicates that, the $S_{Mi,qj}$ predicts both the amount and direction of a deviation that the amount M_i "intends" to undergo as a response to the possible deviation ∂q_j. For instance, the sensitivity of the drug amount M_2 to the absorption rate constant K_a is written as

$$S_{M_2,K_a} = \frac{\partial M_2}{\partial K_a} \qquad (3)$$

The sensitivities "S" are obtainable from the "sensitivity model" (Rosenwasser and Yusupov 2000). Having the sensitivity $S_{Mi,qj}$, the deviation ΔM_i (t) caused by a small deviation Δq_j is calculated as follows

$$\Delta M_i(t) = S_{M_i,q_j}(t)\, \Delta q_j \qquad (4)$$

and the new (i.e. deviated) value of the drug amount M_i will be given by Eq. (5)

$$M_i(t)_{new} = M_i(t) + \Delta M_i(t) \qquad (5)$$

To demonstrate power and feasibility of the method, the two-compartment model (Wagner 1975) shown in Fig. 1 was analysed in detail. By definition, S_{M_1,K_a} predicts possible deviations ΔM_1 (t) induced by a deviation of the absorption rate constant K_a. To compare the predicted deviations with the actual ones, the natrium p-aminosalicylicum (NaPAS) was applied to rats and the nominal concentration profile $M_1(t)$ was recorded. After a wash out period the experiment was repeated but with an addition of the tenside Tween 80, which is known to enhance drug absorption. Parameters were identified from *in vivo* samples by adaptive models (Vitková and Vitko 1993). Obtained time courses of both the nominal M_1, and deviated $M_1 + \Delta M_1$ drug amounts together with the corresponding sensitivity S_{M_1,K_a} are shown in Fig. 2. The continuous curves were obtained by the model while their discrete counterparts (asterisks and squares) were measured *in vivo*. As the records show, the sensitivity S_{M_1,K_a} is positive over the time interval 0–0.65 h, then it falls below zero and remains negative. Thus, the sensitivity function S_{M_1,K_a} predicts that the increased K_a will cause an increase of M_1 at the beginning phase, but after 0.65 hour the amount M_1 will fall under its nominal values (the thin curve). This is in exact correspondence with the *in vivo* experiment. Asterisks and squares represent NaPAS samples with and without Tween 80 respectively. As could be seen, the as-

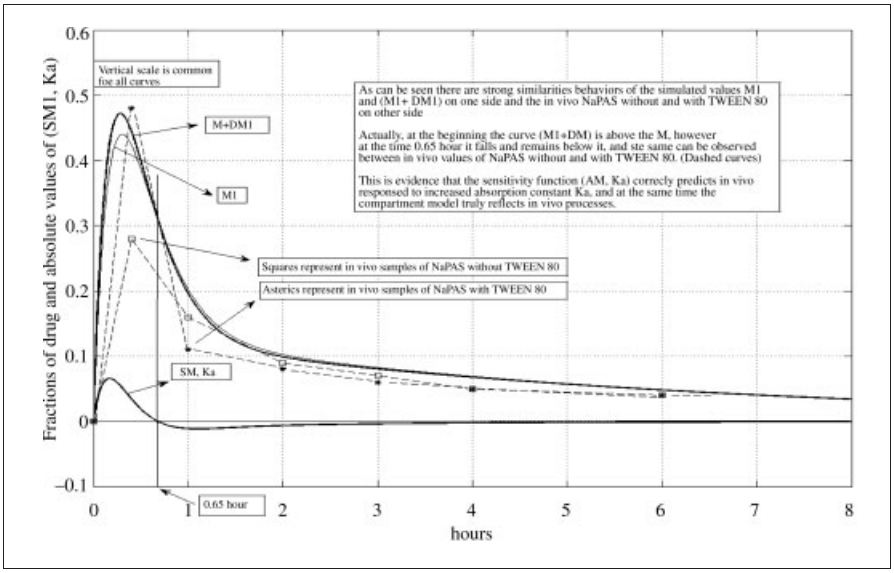

Fig. 2: Results of sensitivity analysis

terisks are above the squares at the beginning but approximately after 0.65 h they actually fall below the squares and remain there. Hence, the sensitivity S_{M_1,K_a} (in Fig. 2 denoted as S_{M_1,K_a}) correctly predicts both the sign and quantity of the deviation $\Delta M_1 = M_1 + \Delta M_1$ (in Fig. 2 denoted as DM_1). The behaviour of the *in vivo* and *in silico* values is the same what validates the model. Consequently, the model validation is a natural by-product of the sensitivity analysis, though it is not enough room here to more complex demonstration of this fact. The approach is general and able to explicitly express relations between the deviation of every single pre-systemic parameter and any chosen *in vivo* response. Low sensitivities indicate that the dissolution test may be considered as a potential waiver of bioequivalence studies.

Acknowledgement: This work was supported by the VEGA Grant Agency of the Slovak Ministry of Education; Grants No. 1/0320/08, No. 1/4295/07, and No.1/3120/06

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Solubility prediction of solutes in aqueous mixtures of ethylene glycols

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Received December 20, 2007, accepted January 26, 2008

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Pharmazie 63: 548–550 (2008)
doi: 10.1691/ph.2008.7856

The applicability of a trained version of the Jouyban-Acree model, for predicting the solubility of solutes in aqueous mixtures of ethylene glycol and its polymerized forms was shown. The solubilities of 8 drugs in binary mixtures were determined and the mean percentage deviation (MPD) was calculated as a prediction accuracy criterion and the overall MPD (± SD) was 23.2 (± 13.1) %

Poorly water-soluble drugs are associated with inadequate and variable bioavailability and ~40% of the new drug candidates possess low aqueous solubility (Liponski 2002). Monomeric and polymeric forms of ethylene glycols were used to enhance the aqueous solubility of drugs in parentral, topical, ophthalmic and oral liquid formulations. In addition, polyethylene glycols are used as excipients in ointments, capsules, pill binders and suppositories (Fruijtier-Pölloth 2005).

The Jouyban-Acree model was developed to calculate different physico-chemical properties in mixed solvent systems which was briefly reviewed (Jouyban et al., 2005). Its basic form to calculate a solute solubility in a binary solvent mixture is:

$$\log X_m = f_c \log X_c + f_w \log X_w + f_c f_w \sum_{i=0}^{2} A_i (f_c - f_w)^i \quad (1)$$

where X_m is the solubility of the solute in solvent mixture, f_c and f_w the volume fractions of cosolvent and water in the absence of the solute, X_c and X_w the solubilities in neat cosolvent and water, respectively, and A_i the solvent-solvent and solute-solvent interaction terms computed using a no-intercept least square analysis for each binary solvent system. The model was extended to Eq. (2) for calculating a solute solubility in binary solvent mixtures at various temperatures (Jouyban-Gharamaleki and Acree 1998) as:

$$\log X_{m,T} = f_c \log X_{c,T} + f_w \log X_{w,T} + f_c f_w \sum_{i=0}^{2} \frac{J_i (f_c - f_w)^i}{T} \quad (2)$$

where $X_{m,T}$, $X_{c,T}$ and $X_{w,T}$ are the solubility of the solute in solvent mixture, cosolvent and water at temperature