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.

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Solubility prediction of solutes in aqueous mixtures of ethylene glycols

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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

Table: Details of the solubility data sets, their references and the mean percentage deviations for the three equations

Drug	Cosolvent	log X_w	log X_c	T (°C)	Reference	log P	MPD		
							eq. (3)	eq. (4)	eq. (5)
Acetaminophen	Polyethylene glycol 200	1.34	2.29	30	Prakongpan and Nagai, 1984	0.51	13.7	35.1	44.9
Chlordiazepoxide	Polyethylene glycol 200	−5.23	−1.63	30	Shokri, 2002	2.85	30.5	71.5	83.7
Clonazepam	Polyethylene glycol 200	−6.07	−1.74	30	Shokri, 2002	2.72	48.2	75.1	82.6
Diazepam	Polyethylene glycol 200	−5.46	−1.46	30	Shokri, 2002	2.99	32.9	73.2	83.3
Lorazepam	Polyethylene glycol 200	−5.46	−1.02	30	Shokri, 2002	2.51	15.3	80.4	84.7
Naphthalene	Ethylene glycol	−3.70	−1.07	25	Khossravi and Connors, 1992	3.30	20.0	37.2	47.4
Phenytoin	Polyethylene glycol 200	1.31	4.87	25	Rubino et al., 1984	2.47	16.8	67.1	78.3
Theophylline	Ethylene glycol	−1.47	−1.26	25	Khossravi and Connors, 1992	−0.02	8.3	27.8	16.3
							23.2	58.4	65.2

(T, K) and J_i is the model constant. Equation (2) was trained using experimental solubility of drugs in water-polyethylene glycol 400 mixtures and the obtained model (Jouyban 2006) was:

$$\log X_{m,T} = f_c \log X_{c,T} + f_w \log X_{w,T} + f_c f_w \times \left[\frac{394.82}{T} - \frac{355.28(f_c - f_w)}{T} + \frac{388.89(f_c - f_w)^2}{T}\right] \quad (3)$$

In deriving Eq. (3), we assumed that the extent of solute-solvent interactions are the same for all solutes in water-polyethylene glycol 400 mixtures. Since ethylene glycols have similar structural features than polyethylene glycol 400, therefore, Eq. (3) is expected to be able to predict the solubility of drugs in aqueous mixtures of ethylene glycols and this hypothesis was examined in this work.

The log-linear model of Yalkowsky (Yalkowsky and Roseman 1981) is a well established cosolvency model providing reasonable predictions. The model required aqueous solubility of the drug (log X_w) and its logarithm of partition coefficient (log P) as input data. The trained version of the model (Li and Yalkowsky 1998) using experimental solubility of drugs in water-polyethylene glycol 400 data was:

$$\log X_m = \log X_w + (0.88 + 0.68 \log P) f_c \quad (4)$$

and the trained model using water-ethylene glycol data was:

$$\log X_m = \log X_w + (0.68 + 0.37 \log P) f_c \quad (5)$$

The accuracy of the proposed method was compared with those of Eqs. (4) and (5).

The mean percentage deviations (MPD) were used to check the accuracy of the prediction method and is calculated using Eq. (6).

$$MPD = \frac{100}{N} \sum \frac{|Calculated - Observed|}{Observed} \quad (6)$$

where N is the number of experimental solubility data.

The Table shows the details of the experimental data sets and the calculated MPD values. The experimental solubility data were reported using different solubility expressions and this widened the range of logarithms of solubilities from negative to positive signs. However, there is no problem with Eq. (3) for predicting the solubilities and the log X_m values will be predicted in the same solubility units which the log X_c and log X_w values were used as input data. The lowest MPD value was observed for theophylline data in water-ethylene glycol mixtures at 25 °C and the highest MPD was obtained for clonazepam data in water-polyethylene glycol 200 at 30 °C. The overall MPD (± SD) was 23.2 ± 13.1 %. This prediction error could be considered as acceptable, since the reasonable error range in solubility correlation was reported as ∼ 30% (Beerbower et al. 1984; Dickhut et al. 1991; Reillo et al. 1995). To show the variations of the individual deviations between predicted and observed solubilities, the log X_m values were plotted as shown in the Fig. The high correlation coefficient between predicted and observed values revealed that the model is capable of predicting the solubilities very close to the observed values from the experiments and could be considered as an accurate prediction tool in practical applications and also in process design. The overall MPD (± SD) for Eqs. (4) and (5) were 58.4 ± 21.2 and 65.2 ± 25.8%, respectively. The mean differences of the MPDs for Eq. (3) were statistically significant for both Eqs. (4) and (5) with the probability level of < 0.001 (paired t-test). The plot of the predicted log X_m by using Eq. (4) *versus* observed values is also shown in the Fig. 1.

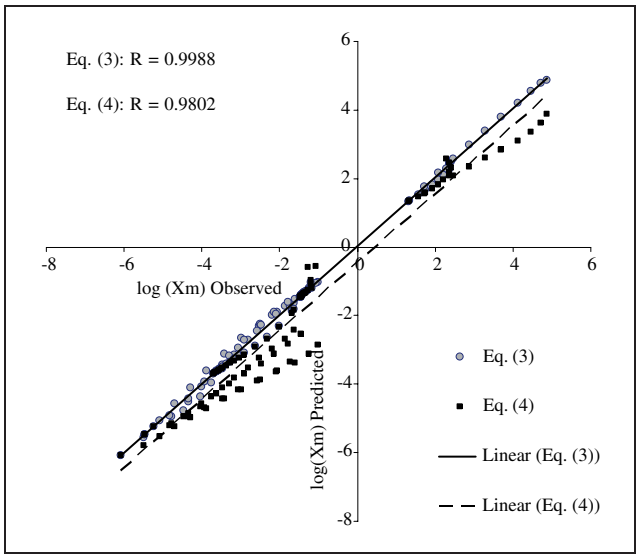

Fig.: Plot of the predicted log Xm values using Eqs. (3) and (4) *versus* observed values

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Erratum to "Quantification of allantoin in various *Zea mays* L. hybrids by RP-HPLC with UV detection" [Pharmazie, 59(2004)524–527]

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In 2004 a detection method for allantoin in Zea mays L. was proposed which contains a significant error regarding the identification of the analyte which is corrected here.

The code for our paper on Quantification of allantoin in various *Zea mays* L. hybrids by RP-HPLC with UV detection, published in volume 59 of this journal contains an error in the identification of analyte. We purposed to find a HPLC method for the determination of allantoin in corn silk. A literature study revealed the analysis of allantoin in this herb by RP-HPLC (Maksimovic et al. 2004). We tried to use this method and observed that the peak of acetone solvent has been mis-identified as allantoin in both the extract and standard solutions. That error is reflected below.

The chromatograms of silk extract and standard solution of allantoin (5 μg/ml) obtained following the above method are identical to the presented chromatograms by Maksimovic et al (Figs. 1 and 2). The UV spectrum of the peak at 4.7 min in the chromatograms of Figs. 1 and 2 was obtained by detector K-2600. The wavelength of absorption maximum was 266 nm. This method suggests the water-acetone (3 : 7 v/v) mixture for dissolving of the allantoin and extracting as solvent. For acquiring of HPLC chromatogram and UV spectrum of the solvent used in the sample preparation and standard solution, water of

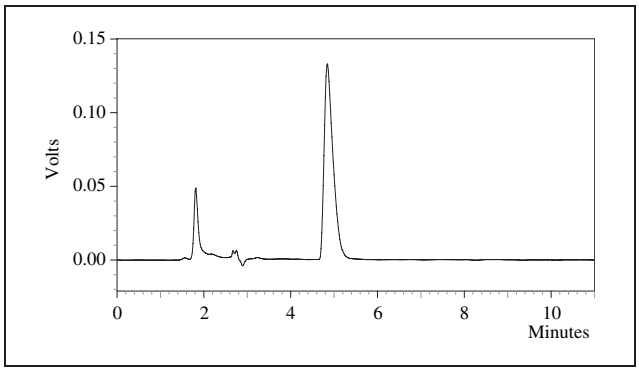

Fig. 1: Chromatogram of silk extract analyzed following the Maksimovic et al. method on an Econosil column at 235 nm