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Solubility prediction of salmeterol xinafoate in water–dioxane mixtures

A. Jouyban-Gharamaleki [a,*], P. York [b], M. Hanna [c], B.J. Clark [a]

[a] *Drug Design Group, School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK*
[b] *Drug Delivery Group, School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK*
[c] *Bradford Particle Design, 49 Listerhills Science Park, Campus Road, Bradford BD7 1HR, UK*

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Abstract

The mole fraction solubility of salmeterol xinafoate was determined in various concentrations of dioxane in aqueous binary mixture. Maximum solubility was observed in 90% v/v dioxane and solubility parameter of the solute was estimated from solubility peak equal to 24.99 $MPa^{0.5}$. The predicting capability of four different cosolvency models was also evaluated employing a five data point training set. The solubility data at other cosolvent concentrations were predicted using the trained models, with percentage average errors for 28 drug solubility data sets in water–cosolvent mixtures lying between 12.5 and 15.0%. Further predictive model is proposed for accurate solubility predictions based on a minimum number of experiments. The percentage average error where tested was 10.6%. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Cosolvency; Solubility; Water–Dioxane; Salmeterol Xinafoate

1. Introduction

Salmeterol is a long acting selective β_2-adrenoceptor agonist, which is indicated for the maintenance treatment of adults and children with asthma with duration of bronchdilation effect at least 12 h. The long duration of action of salmeterol makes it suitable drug for the treating patients with nocturnal asthma and improves their sleep quality. Salmeterol is formulated as lung delivery formulations (Adkins and McTavish, 1997) as a xinafoate salt that dissociates in solution to salmeterol and 1-hydroxy-2-naphthalate (xinafoate).

The most common technique for dissolving a poorly water-soluble drug is to add a water miscible cosolvent. In order to find the optimum cosolvent concentration to dissolve the drug, pharmaceutical scientists often carry out a large number of experiments. From this empirically based approach, numerous cosolvency models have been proposed for calculating drug solubility

* Corresponding author. Present address: Faculty of Pharmacy, The University of Sydney, Sydney N.S.W. 2006, Australia. Tel.: +61-2935-18586; fax: +61-2935-14391.

E-mail address: ghasem@pharm.usyd.edu.au (A. Jouyban-Gharamaleki).

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in water–cosolvent mixtures (Martin et al., 1980; Ochsner et al., 1985; Acree, 1992; Barzegar-Jalali and Jouyban-Gharamaleki, 1997; Jouyban-Gharamaleki, 1998). These models can be categorised into two groups, i.e. predictive models and correlative equations. The principal advantage of the predictive models, such as the universal functional group activity coefficient (UNIFAC), is that experimental data are not required. The UNIFAC model has shown some success in estimating solid solubility in mixed solvents from chemical structure information (Acree, 1983). The correlative equations, such as the combined nearly ideal binary solvent/Redlich–Kister (Acree, 1992), employ curve-fitting parameters to correlate experimental solubility data with respect to the concentration of the cosolvent. In order to calculate these curve-fitting parameters, a set of experiments in mixed solvents is determined to train the model. The quality of curve-fitness of the available cosolvency models has been evaluated using 30 sets of different drug solubility data in various water-cosolvent systems (Jouyban-Gharamaleki et al., 1999) and the results showed that most of the models produced reasonably accurate results (percent average error between 3.1 and 7.8%).

From a practical point of view, the minimum number of curve-fitting parameters provides the best cosolvency model, because it needs a minimum number of experiments as a training set to calculate the curve-fitting parameters. In this work, the predictive capability of the correlative cosolvency models based on experimental solubility data at 0, 0.3, 0.6, 0.9 and 1 volume fractions of the cosolvent is presented. The solubility data of salmeterol xinafoate in water–dioxane mixture from this work together with sets of solubility data collected from the pharmaceutical literature are examined.

2. Theoretical treatment

The curve-linear relationship between the logarithm of the mole fraction solubility (X_m) in different concentration of the cosolvent can be correlated by a power series of the volume fraction of the cosolvent (f_c). This model has been presented as an empirical equation by Wu and Martin (1983) and a theoretical justification has been provided recently (Barzegar-Jalali and Jouyban-Gharamaleki, 1997). The model is:

$$\ln X_m = A_0 + A_1 f_c + A_2 f_c^2 + A_3 f_c^3 \quad (1)$$

where A_0–A_3 are the curve-fitting parameters. Higher degrees of polynomial function can be employed to correlate the experimental data accurately.

The statistically based mixture response model was introduced by Ochsner et al. (1985). The authors showed that the mixture response model produced more accurate results in comparison with the results of the extended Hildebrand solubility approach (Ochsner et al., 1985). The mixture response model is:

$$\ln X_m = B_1 f'_c + B_2 f'_w + \frac{B_3}{f'_c} + \frac{B_4}{f'_w} + B_5 f'_c f'_w \quad (2)$$

where f'_c and f'_w are the modified volume fractions of the cosolvent and water which calculated by $f' = 0.96\ f + 0.02$ and B_1–B_5 denote the curve-fitting parameters.

The combined nearly ideal binary solvent/Redlich–Kister equation was derived from the thermodynamic mixing model of Hwang et al. (1991). The mixing model includes contributions from two-body and three-body interactions. By differentiating the Gibbs free energy expressions of a ternary solution with respect to the number of moles of the solute, the combined nearly ideal binary solvent/Redlich–Kister equation was derived (Acree, 1992) as:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w [M_0 + M_1 (f_c - f_w) + M_2 (f_c - f_w)^2], \quad (3)$$

where X_c and X_w are the mole fraction solubility in pure cosolvent and water and M_0–M_2 denote the curve-fitting parameters representing solute–solvent and solvent–solvent interactions (Acree, 1992). These parameters can be calculated by two procedures:

1. regressing $(\ln X_m - f_c \ln X_c - f_w \ln X_w)/f_c f_w$ against $f_c - f_w$ and $(f_c - f_w)^2$ by a classical least square analysis (Acree et al., 1991);
2. regressing $\ln X_m - f_c \ln X_c - f_w \ln X_w$ against $f_c f_w$, $f_c f_w (f_c - f_w)$ and $f_c f_w (f_c - f_w)^2$ by a no intercept least square analysis (Jouyban-Gharamaleki and Hanaee, 1997). This procedure produced more accurate correlations for the solute's solubility in aqueous binary solvent.

The original model was derived based on the mole fractions of the solvents rather than the volume fractions. However, the volume fraction based form of the equation is derivable by approximating the weighting factor with molar volumes.

The fourth model to be considered is the modified Wilson equation (Jouyban-Gharamaleki, 1998). This model contains two curve-fitting parameters and is expressed as:

$$-\ln X_m = 1 - \frac{f_c (1 + \ln X_c)}{f_c + \lambda_1 f_w} - \frac{f_w (1 + \ln X_w)}{\lambda_2 f_c + f_w}, \quad (4)$$

where λ_1 and λ_2 are the adjustable parameters which can be computed by a GW-BASIC pc program (see Appendix A). Since λ_1 and λ_2 represent the interaction terms in the solution, the numerical values should be greater than zero. It should be noted that there are several λ_1 and λ_2 parameter pairs, which describe the solute solubility within reasonable PAE values and these numerical values affect the prediction capability of the model. Thus the optimised values are preferred to achieve the best predictions. The maximum λ_1 and λ_2 values for 30 different solubility sets in water–cosolvent mixtures were 26.39 and 3.29, respectively (Jouyban-Gharamaleki, 1998). Therefore, the maximum values of λ_1 and λ_2 are chosen equal to 30 and 4 in this study.

Since the various models predict different solubility values for a drug, i.e. some of them produced overestimated values and the others underestimated solubilities, the mean predicted solubility (MPS) at each volume fraction is also calculated:

$$\mathrm{MPS} = \left[\frac{(X_m)_1 + (X_m)_2 + (X_m)_3 + (X_m)_4}{4}\right], \quad (5)$$

where $(X_m)_1$, $(X_m)_2$, $(X_m)_3$ and $(X_m)_4$ are the predicted mole fractions solubilities by Eqs. (1)–(4), respectively.

3. Materials and methods

Salmeterol xinafoate was supplied by Glaxo Wellcome (Ware, UK), 1,4-dioxane and methanol were purchased from BDH (Poole, UK) and double distilled water was used in this work. A slight excess of salmeterol xinafoate powder was equilibrated with the pure or mixed solvent in a fixed temperature room at 19 ± 0.1°C. The solutions were agitated by using a shaker under a constant rate. After 72 h, the non-dissolved solid phase was removed by filtration (0.2 μm pore size, NLG Analytical, UK). The densities of the saturated solutions were determined in a 10 ml density bottle. The clear solutions were diluted with water–methanol (50:50% v/v) and assayed by a spectrophotometer at 250 nm. The solvent mixtures were prepared by mixing the appropriate volumes of dioxane and double distilled water. All experimental results are the average of three replicated experiments. The relative standard deviation is within 3% among replicated samples.

The solubility data at 0, 0.3, 0.6, 0.9 and 1 volume fractions of the cosolvent were employed as the training set. Then the calculated model constants from training sets were employed to predict the solubility at other volume fractions of the colsolvent. The correlation/prediction capability of the models was evaluated by percent average error (PAE) which calculated by:

$$\mathrm{PAE} = \frac{1}{N}\sum_{1}^{N}\frac{|\mathrm{Calculated} - \mathrm{Observed}|}{\mathrm{Observed}}, \quad (6)$$

where N is the number of data points. All calculations were performed by SPSS software. The adjustable parameters of Eq. (4) were computed by a GW-BASIC program.

4. Results and discussion

The logarithm of the mole fraction solubility of salmeterol xinafoate and the back-calculated solu-

Table 1
The experimental solubility of salmeterol xinafoate in water–dioxane [a] mixtures at 19°C and the back-calculated solubility values by different equations

f_c	ln X_2 [b]	Equation				
		Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	Eq. (5)
0.00	−5.5564	−5.4854	−5.5463	−5.5564	−5.5564	−5.5357
0.10	−5.0146	−5.0482	−5.1247	−4.9336	−4.9020	−4.9982
0.20	−4.4398	−4.5214	−4.4276	−4.4173	−4.3114	−4.4166
0.30	−3.8726	−3.9246	−3.7786	−3.9087	−3.7764	−3.8446
0.40	−3.2910	−3.2903	−3.1942	−3.3574	−3.2910	−3.2815
0.50	−2.7328	−2.6643	−2.6791	−2.7606	−2.8508	−2.7360
0.60	−2.2064	−2.1051	−2.2363	−2.1640	−2.4535	−2.2313
0.70	−1.6990	−1.6845	−1.8703	−1.6609	−2.1010	−1.8141
0.80	−1.5066	−1.4872	−1.5924	−1.3929	−1.8061	−1.5581
0.90	−1.4688	−1.6110	−1.4500	−1.5496	−1.6302	−1.5577
0.95	−1.6594	−1.8274	−1.5175	−1.8595	−1.6890	−1.7140
1.00	−2.3685	−2.1667	−2.3989	−2.3685	−2.3685	−2.3212
	PAE	7.99	7.10	5.80	12.12	3.94

[a] Dioxane is a toxic solvent and is not allowed to add to the pharmaceutical formulations. However, because of its miscibility with water and lower polarity, it can be used as a model cosolvent in pharmaceutical studies.
[b] Average of three replicated experiments. The relative standard deviation is within 3%.

bility data in different volume fractions of dioxane are shown in Table 1. The salmeterol xinafoate solubility increases with an increase in dioxane concentration in the mixture, then it reaches to a maximum value at $f_c = 0.90$ and decreases with further increase in dioxane concentration. These data were fitted to the equations and the model constants were computed based on whole data points. The fitness ability of the equations is evaluated by comparing PAE values. The accuracy order of the equations is Eq. (5) > Eq. (3) > Eq. (2) > Eq. (1) > Eq. (4). The accuracy pattern for Eqs. (1)–(3) was also confirmed where 30 different solubility sets in water–cosolvent mixtures were used for comparing the models (Jouyban-Gharamaleki et al., 1999). Since Eq. (3) produced the most accurate results (Jouyban-Gharamaleki et al., 1999), a solubility curve by Eq. (3) versus the solvent's solubility parameter (δ_1) was plotted (Fig. 1). From this the solubility parameter of salmeterol xinafoate (δ_2) was estimated equal to the δ_1 in solubility maximum with $\delta_2 = 24.99$ MPa$^{0.5}$. The solute solubility parameter is an intrinsic physicochemical property, which has been employed to explain drug action (Mullins, 1954), drug transport kinetics (Khalil and Martin, 1967), structure activity relationship (Khalil et al., 1976a,b), drug–plasma protein binding (Bustamante and Sellés, 1986) and the tablet process (Rowe, 1988). The pharmaceutical applications of solubility parameters were reviewed recently (Hancock et al., 1997).

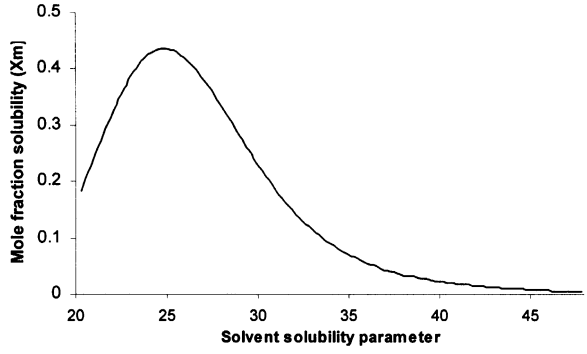

Fig. 1. Plot of salmeterol xinafoate mole fraction solubility in water–dioxane mixtures versus the mixed solvent solubility parameter (δ_1). (a) Solvent solubility parameter (δ_1) is calculated by $\delta_1 = f_c\delta_{\text{Cosolvent (c)}} + f_w\delta_{\text{Water (w)}}$ where $\delta_c = 20.3$ and $\delta_w = 46.87$ MPa$^{1/2}$ are taken from Beerbower et al. (1984). Maximum solubility is at $f_c = 0.83$ thus solubility parameter of the solute is $\delta_2 = 24.99$ MPa$^{1/2}$.

Table 2
The experimental and predicted salmeterol xinafoate solubility by using five data point training set[a] for different equations

f_c	ln X_2	Equation				
		Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	Eq. (5)
0.10	−5.0146	−5.1062	−5.3717	−4.8260	−4.9507	−5.0436
0.20	−4.4398	−4.5753	−4.5986	−4.3204	−4.3908	−4.4642
0.40	−3.2910	−3.3034	−3.2288	−3.3818	−3.3925	−3.3244
0.50	−2.7328	−2.6502	−2.6720	−2.8152	−2.9488	−2.7644
0.70	−1.6990	−1.6381	−1.8404	−1.6560	−2.1723	−1.8050
0.80	−1.5066	−1.4546	−1.5809	−1.3319	−1.8568	−1.5378
0.95	−1.6594	−1.8858	−1.5561	−1.8018	−1.7025	−1.7289
	PAE	9.02	12.66	12.40	16.02	4.50

[a] The training set includes the solubility of salmeterol xinafoate at 0, 0.3, 0.6, 0.9 and 1 volume fractions of dioxane.

The experimental and predicted salmeterol xinafoate solubilities using five data points and the corresponding PAE values are given in Table 2 (see also Appendix B). The accuracy order is Eq. (5) > Eq. (1) > Eq. (3) > Eq. (2) > Eq. (4). The prediction error levels can be considered as reasonable errors particularly in pharmaceutical applications where percentage error less than 30% has been considered as an acceptable error (Beerbower et al., 1984; Reillo et al., 1995).

In order to provide more evidence for the accuracy and reliability of solubility prediction based on five data points training sets, 28 different solubility data in water–cosolvent mixtures collected from the pharmaceutical literature. The detail of the data and PAE for the predicted solubilities by different equations is shown in Table 3. The accuracy order for the models studied was Eq. (5) > Eq. (3) > Eq. (1) > Eq. (2) > Eq. (4). In order to investigation further the predictability of the models, the Pearson's correlation coefficient between the experimental mole fraction solubilities and the predicted values by different equations were computed. The r values were 0.984, 0.994, 0.988, 0.986 and 0.995 for Eqs. (1)–(5), respectively.

In conclusion, the MPS approach produced the most accurate predictions. It is suggested that for ab initio experiments for prediction purposes, the volume fractions with equal intervals, i.e. 0, 0.25, 0.50, 0.75 and 1 can be used. It is expected that this set is able to produce acceptable predictive cosolvency model constants. Although a large number of solubility data of non-pharmaceutical compound in non-aqueous solvent mixtures have been published in the literature, the number of drug solubility data in water–cosolvent mixtures is limited. The present study extends the database on the drug solubility in aqueous binary solvents. With this a pharmaceutical scientist can develop more comprehensive cosolvency models to provide more confident predictions and theories. From a practical point of view, the cosolvency models can be employed for rational approaches to pharmaceutical formulation.

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Table 3
Percent average error (PAE) for Eqs. (1)–(5) of predicted solubility data collected from the literature

System No.	Cosolvent	Solute	Reference	N[a]	Equation				
					Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	Eq. (5)
1	Dimethylformamide	Caffeine	Herrador and Gonzalez, 1997	6	13.0	11.2	10.6	10.5	9.6
2	Dioxane	Caffeine	Adjei et al., 1980	11	11.5	2.8	12.2	14.6	7.8
3	Dioxane	Paracetamol	Romero et al., 1996	12	12.9	9.1	11.2	11.9	7.3
4	Dioxane	Phenacetin	Bustamante and Bustamante, 1996	8	17.6	16.3	10.9	4.4	8.3
5	Dioxane	Sulphadiazine	Bustamante et al., 1993	12	19.2	17.2	18.3	14.7	9.7
6	Dioxane	Sulphadimidine	Bustamante et al., 1993	14	16.8	6.0	22.1	11.9	11.0
7	Dioxane	Sulphamethizole	Reillo et al., 1995	14	30.3	15.9	29.7	14.7	16.0
8	Dioxane	Sulphamethoxazole	Bustamante et al., 1993	10	20.7	28.4	22.3	5.5	15.9
9	Dioxane	Sulphamethoxypyridazine	Bustamante et al., 1993	13	20.1	11.3	14.2	11.1	9.5
10	Dioxane	Sulphanilamide	Reillo et al., 1993	11	14.0	5.2	18.1	10.4	9.2
11	Dioxane	Sulphasomidine	Martin et al., 1985	16	18.7	6.8	19.4	14.6	8.7
12	Dioxane	Theobromine	Martin et al., 1981	6	3.6	4.9	3.1	3.7	3.7
13	Dioxane	Theophylline	Martin et al., 1980	16	16.1	2.6	22.4	15.1	7.4
14	Ethanol	Furosemide	Jouyban-Gharamaleki et al., 1998	8	15.0	27.0	9.3	39.6	15.2
15	Ethanol	Oxolinic acid	Jouyban-Gharamaleki et al., 2000	6	15.5	7.9	1.9	17.8	10.6
16	Ethanol	Paracetamol	Romero et al., 1996	8	10.1	7.5	10.8	7.9	7.8
17	Ethanol	Sulphamethazine	Bustamante et al., 1994	6	13.5	6.9	7.2	16.5	10.4
18	Ethanol	Sulphanilamide	Bustamante et al., 1994	7	4.3	7.1	4.8	5.2	4.6
19	Glycerol	Furosemide	Jouyban-Gharamaleki et al., 1998	7	4.4	17.0	10.1	6.6	8.9
20	Propylene glycol	Butyl *p*-aminbenzoate	Rubino and Obeng, 1991	6	11.1	13.6	10.8	15.4	8.1
21	Propylene glycol	Butyl *p*-hydroxybenzoate	Rubino and Obeng, 1991	6	18.8	34.5	9.2	39.0	21.8
22	Propylene glycol	Ethyl *p*-aminobenzoate	Rubino and Obeng, 1991	6	4.2	13.8	6.5	12.5	9.2
23	Propylene glycol	Ethyl *p*-hydroxybenzoate	Rubino and Obeng, 1991	6	7.6	21.2	10.1	18.3	13.3
24	Propylene glycol	Furosemide	Jouyban-Gharamaleki et al., 1998	8	18.1	37.3	21.1	32.0	26.7
25	Propylene glycol	Methyl *p*-aminobenzoate	Rubino and Obeng, 1991	6	5.1	11.0	5.5	8.6	7.3
26	Propylene glycol	Methyl *p*-hydroxybenzoate	Rubino and Obeng, 1991	6	5.5	19.7	8.7	19.7	8.1
27	Propylene glycol	Proply *p*-aminobenzoate	Rubino and Obeng, 1991	6	8.6	15.6	9.4	14.3	12.0
28	Propylene glycol	Proply *p*-hydroxybenzoate	Rubino and Obeng, 1991	6	10.4	18.4	10.2	22.4	9.9
				Mean:	13.1	14.2	12.5	15.0	10.6

[a] *N* is the number of predicted data points.

Appendix A

```
10  REM ********* CALCULATION OF MODIFIED WILSON'S PARAMETERS ***********
20  COLOR 2,1,4:CLS:COLOR 2,0:KEY OFF:N=5:AE=1000
30  STEP1=.1 : STEP2 =.1 : MINI=.1 : MINJ=.1
40  LOCATE 10,15:INPUT "Enter maximum value of lamda1 (30)";MAXI
50  LOCATE 12,15:INPUT "Enter maximum value of lamda2 (4)";MAXJ
60  COLOR 2,1,4:CLS:II=250:DIM FC(II),XM(II),XC(II),XW(II),FW(II)
70  FOR Q=1 TO N:READ FC(Q),XM(Q),XC(Q),XW(Q):FW(Q)=1-FC(Q):NEXT Q
80  COLOR 14,4:LOCATE 6,12:PRINT " Optimum Values : ":COLOR 2,0 :LOCATE 13,12:PRINT " Current Values : "
90  COLOR 0,7:LOCATE 19,12:PRINT "   First digit optimisation of lamda1 and lamda2    ":COLOR 2,0
100 GOSUB 330
110 COLOR 0,7:LOCATE 19,12:PRINT "   Second digit optimisation of lamda1 and lamda2    ":COLOR 2,0
120 LL=LL+1:SM=.1*G1B-.01*G1B*LL: LV=.1*G2B-.01*G2B*LL
130 MINI=G1B-SM :MAXI=G1B+SM :STEP1=(MAXI-MINI)/10:MINJ=G2B-LV:MAXJ=G2B+LV:STEP2=(MAXJ-MINJ)/10
140 LOCATE 20,2:PRINT USING " lamda1: Min=##.####    Max=##.####    Step=#.#### Sm=#.####";MINI,MAXI,STEP1,SM
150 LOCATE 21,2:PRINT USING " lamda2: Min=##.####    Max=##.####    Step=#.#### Lv=#.####";MINJ,MAXJ,STEP2,LV
160 NNN=NNN+1:LOCATE 22,20:PRINT USING " No. of repeatation=##";NNN
170 IF STEP1 <.0001 AND STEP2<.0001 THEN 200
180 GOSUB 330
190 GOTO 120
200 SM=G1B*.001:LV=G2B*.001:MINI=G1B-SM :MAXI=G1B+SM :STEP1=.0001: MINJ=G2B-lV:MAXJ=G2B+LV:STEP2=.0001
210 LOCATE 20,2:PRINT USING " lamda1: Min=##.####    Max=##.####    Step=#.#### Sm=#.####";MINI,MAXI,STEP1,SM
220 LOCATE 21,2:PRINT USING " lamda2: Min=##.####    Max=##.####    Step=#.#### Lv=#.####";MINJ,MAXJ,STEP2,LV
230 COLOR 0,7:LOCATE 19,12:PRINT "   Fourth digit optimisation of lamda1 and lamda2    ":COLOR 2,0
240 GOSUB 330
250 CLOSE :BEEP
260 COLOR 2,1,14:CLS:COLOR 2,0:LOCATE 10, 15: PRINT " The optimised modified Wilson model is: "
270 LOCATE 12,15:PRINT "          fc(1 -";:PRINT USING "##.####)     fw(1 -##.####)   ";LOG(1/XC(1)),LOG(1/XW(1))
280 LOCATE 13,15:PRINT " lnXm = 1 - ";STRING$(17,196);" - ";STRING$(17,196);" "
290 LOCATE 14,15:PRINT "          fc + ";:PRINT USING "##.####fw     ##.####fc + fw   ";G1B,G2B
300 END
310 REM ------------------------------------------------------------------------
320 REM ------- Minimisation of the PAE values -----------------------------
330 FOR G1 =MINI TO MAXI STEP STEP1
340 FOR G2 =MINJ TO MAXJ STEP STEP2
350 E=0:SE=0:ER=0:SPER=0:QPER=0
360 FOR I=1 TO N
370 Y=1/EXP(1-((FC(I)*(1+LOG(XC(I))))/(FC(I)+FW(I)*G1)) -((FW(I)*(1+LOG(XW(I))))/(FW(I)+FC(I)*G2)))
380 Q=1/EXP(1-((FC(I)*(1+LOG(XC(I))))/(FC(I)+FW(I)*G2)) -((FW(I)*(1+LOG(XW(I))))/(FW(I)+FC(I)*G1)))
390 QER=ABS(100*(Q-XM(I))/XM(I)):QPER=QPER+QER :PER=ABS(100*(Y-XM(I))/XM(I)):SPER=SPER+PER
400 NEXT I
410 E=SPER/N:W=QPER/N
420 IF E=<AE THEN COLOR 14,4:AEE=E:AE=E:G1B=G1:G2B=G2: LOCATE  8,10:PRINT USING " PAE = ###.##  lamda1= ##.####  lamda2= ##.####";AE,G1B,G2B:COLOR 2,0
430 IF W=<AE THEN COLOR 15,4:AEW=W:AE=W:G1B=G2:G2B=G1:LOCATE  9,10:PRINT USING " PAE = ###.##  lamda1= ##.####  lamda2= ##.####";AE,G1B,G2B:COLOR 2,0
440 LOCATE 15,10:PRINT USING " PAE = ###.##  lamda1= ##.####  lamda2= ##.####";E,G1,G2
450 NEXT G2
460 NEXT G1
470 RETURN
480 REM ------------------------------------------------------------------------
490 REM  5 data points - salmeterol xinafoate solubility in water-dioxane
500 REM --fc-----Xm----------Xc----------Xw--------------------------------
510 DATA 0.00 ,0.00386263 , 0.09362401 , 0.00386263
520 DATA 0.30 ,0.02080503 , 0.09362401 , 0.00386263
530 DATA 0.60 ,0.11009742 , 0.09362401 , 0.00386263
540 DATA 0.90 ,0.23020526 , 0.09362401 , 0.00386263
550 DATA 1.00 ,0.09362401 , 0.09362401 , 0.00386263
```

Appendix B

Salmeterol xinafoate solubility calculation's detail:

The model constants of the Eqs. (1)–(4) were calculated based on the five data points training set by using a program in SPSS environment and also a GW-BASIC program. The resulted equations are:

$$\ln X_m = -5.533 + 3.711 f_c + 5.632 f_c^2 - 6.091 f_c^3, \quad (7)$$

$$\ln X_m = -1.148 f'_c - 6.545 f'_w + \frac{0.018}{f'_c} - \frac{0.025}{f'_w} + 4.953 f'_c f'_w, \quad (8)$$

$$\ln X_m = -5.556 f_c - 2.369 f_w + f_c f_w [4.589 + 5.603 (f_c - f_w) + 6.980 (f_c - f_w)^2], \quad (9)$$

$$-\ln X_m = 1 - \frac{f_c(1 - 5.556)}{f_c + 29.453 f_w} - \frac{f_w(1 - 2.369)}{1.393 f_c + f_w} \quad (10)$$

The solubilities of salmeterol xinafoate at other f_c values were predicted by Eqs. (7)–(10). Average of 4 solubility values at each f_c predicted by Eqs. (7)–(10) is considered as the MPS. As an example, the predicted solubilities at $f_c = 0.5$ are: Eq. (7): $\ln X_m = -2.650$, Eq. (8): $\ln X_m = -2.672$, Eq. (9): $\ln X_m = -2.815$ and Eq. (10): $\ln X_m = -2.949$. MPS is $(0.07383850 + 0.06917955 + 0.05989348 + 0.05240490)/4$ or 0.06382911. The numerical values of the salmeterol solubility data are as:

f_c	X_m	Eq. (1)	Eq. (2)	Eq. (3)	Eq. (4)	Mean of Eqs. (1)–(4)
0.10	0.00664012	0.00568990	0.00464958	0.00801876	0.00707824	0.00635912
0.20	0.01179787	0.00983012	0.01007344	0.01329431	0.01239048	0.01139709
0.40	0.03721674	0.03801281	0.03964072	0.03398597	0.03362419	0.03631592
0.50	0.06503988	0.07383850	0.06917955	0.05989348	0.05240490	0.06382911
0.70	0.18286567	0.19072761	0.15900195	0.19090488	0.11391633	0.16363769
0.80	0.22166954	0.22010381	0.20626344	0.26398048	0.15617007	0.21162945
0.95	0.19024564	0.14776112	0.21245165	0.16500094	0.18223166	0.17686134

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