AN ARTIFICIAL NEURAL NETWORK MODEL FOR THE PREDICTION OF THE SOLUBILITY OF FOUR NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN SUPERCRITICAL CARBON DIOXIDE.

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Abstract - Artificial neural networks (ANN) are applied to literature data in order to develop and validate a model that can predict the solubility of four non-steroidal anti-inflammatory drugs (flurbiprofen, ibuprofen, ketoprofen and naproxen) in supercritical carbon dioxide ($scCO_2$). A multilayer feedforward backpropagation network is used with three hidden layers. The model has five inputs (two intensive state variables and three pure drug properties) and one output (solubility of solid drug in $scCO_2$). The network is systematically trained with 96 data points in the temperature and pressure ranges (308.15-333.1K), (8-25 MPa) respectively and is validated with 47 data points. Different combinations of network architectures, training algorithms and learning parameters are attempted. The training and validation strategy is based on the use of a validation agreement vector, determined from linear regression analysis of the plots of the predicted versus experimental of the solubility of solid drug in $scCO_2$, as a measure of the predictive ability of the ANN model. Statistical analysis of the predictability of the neural networks model shows excellent agreement with experimental data. Furthermore, the comparison in terms of average absolute relative deviation between the predicted results for each binary for the whole temperature range and literature results predicted by some cubic equation of state with various mixing rules shows that the ANN model gives comparable and even better results. In contrast to equation of state the ANN model does not necessitate the sublimation pressure and the molar volume of the solid solute.
Keywords: Solubility; Artificial neural networks; Anti-inflammatory drugs; Supercritical Carbon dioxide.

INTRODUCTION

The pharmaceutical industry like many other process industries has witnessed over the last decades an increasing level of interest in supercritical fluid (SCF) technology. Conventional production processes of many drugs comprise a series of multiple separation and purification operations involving a series of organic solvent extraction and precipitation steps and finish with the recovery of large amount of organic solvents. Supercritical fluid technologies are considered as a promising alternative to replace conventional processes while environmentally benign, less energy intensive, more effectively controlling product specification and less costly. Supercritical carbon dioxide ($ScCO_2$) can replace toxic and undesirable organic solvents which either require extensive solvent recovery units or remain in very small but still dangerous proportions. The most decisive and critical factor affecting the efficacy and the correspondent technical and economical success of most SCF processes is the accurate knowledge of the equilibrium solubility of the materials to be processed in the selected SCF solvent and/or the solubility of that SCF in those materials. Most commonly, the solubility of a solid in a SCF phase is correlated using empirical and semi-empirical models based on density of the SCF, pressure and temperature and equations of state (EoS)[1]. While extensive experimental data of solubility of biomolecules and pharmaceutical compounds in supercritical fluids are being published, attempts of modeling for the purpose of prediction, using EoS and empirical

models, are however still not satisfactory to the desired level of accuracy. Moreover, the large number of EoS and their mixing that exist in the literature, makes their use far from safe and easy. On the other hand artificial neural networks (ANN), which can be viewed as universal approximation tool with an inherent ability to extract from experimental data the highly non linear and complex relationships between the variables of the problem handled, have gained broad attention within process engineering as a robust and efficient computational tool. As far as solubility and phase equilibria are concerned, Tabaraki et al.[2] have used a wavelet NN to predict the solubility of azo dyes in $scCO_2$ and Tabaraki et al.[3] of 25 anthraquinone dyes in $scCO_2$ at different conditions of temperature and pressure. Si-Moussa et al.[4] have used a feedforward NN to predict high-pressure vapor liquid equilibrium of six CO_2-ester binaries. In this work an attempt was made to estimate the solubility of four non-steroidal anti-inflammatory drugs (flurbiprofen, ibuprofen, ketoprofen and naproxen) in $scCO_2$ using a single ANN predictive model.

The experimental data reported by Stassi et al.[5] for CO_2-Ketoprophen, Ting et al.[6] for CO_2-Naproxen, Charoenchaitrakool et al.[7] for CO_2-Ibuprophen and Duarte et al.[8] for CO_2-Flurbiprohpen systems, have been used for training and validation of the ANN model. The pure component properties of the four drugs used in this work are listed in Table 1. For flurbiprohen three data sets are used, as in the work of Coimbra et al.[1], due to the different methods used to predict the critical properties and the acentric factor of flurbiprohen. The range of the intensive state variables and the number of data points for each binary are listed in Table 2.

Table 1: Pure component properties used in this work.

Component	T_c (K)	P_c (MPa)	ω	Reference
Ketoprophen	1090.7	2.584	0.914	Coimbra et al.[1]
Naproxen	807.0	2.452	0.904	Coimbra et al.[1]
Ibuprophen	749.7	2.330	0.819	Coimbra et al.[1]
Flurbiprophen (Set1)	987.0	2.500	0.933	Coimbra et al.[1]
Flurbiprophen (Set2)	830.4	2.401	0.967	Coimbra et al.[1]
Flurbiprophen (Set3)	830.4	2.401	0.671	Coimbra et al.[1]

Table 2: Data source and range used for training and validation of the artificial neural network model.

System	T (K)	P (MPa)	$10^5.y_2$	N	Reference
CO_2-Ketoprophen	313	9-25	0.39-9.15	7	Stassi et al.[5]
	328	11-25	0.33-18.8	8	Stassi et al.[5]
CO_2-Naproxen	313.1	8.96-19.31	0.2-2.43	6	Ting et al.[6]
	323.1	10-19.31	0.19-2.91	6	Ting et al.[6]
	333.1	12.41-19.31	0.7-3.18	6	Ting et al.[6]
CO_2-Ibuprophen	308.15	8-22	5.3- 441	15	Charoenchaitrakool et al.[7]
	313.15	9.5-22	58.5- 649	6	Charoenchaitrakool et al.[7]
	318.15	8.5-17	3 - 584	8	Charoenchaitrakool et al.[7]
CO_2- Flurbiprophen	303	8.9-24.5	2.17 – 8.337	11	Duarte et al.[8]
	313	9.8-24.4	1.672 - 14.95	9	Duarte et al.[8]
	323	11.2-23.4	2.603 - 19.683	7	Duarte et al.[8]
The whole data set	308.15-333.1	8-25	0.7 - 649	143	

SOLUBILITY MODELING WITH NEURAL NETWORK

In order to describe the phase behavior of the four CO_2(1)-NSAID(2) binaries by one ANN model a total of six variables have been selected in this work: three intensive state variables (equilibrium temperature, equilibrium pressure and the solubility of the solid drug in SCF phase) and three pure component properties of the NSAID (critical temperature, critical pressure and acentric factor). The equilibrium temperature (T), the equilibrium pressure (P) and the pure component properties of the solid drug (T_c, P_c and ω) have been selected as input variables and the mole fraction solubility of the solid drug in the SCF phase as the output variable (Fig.1).

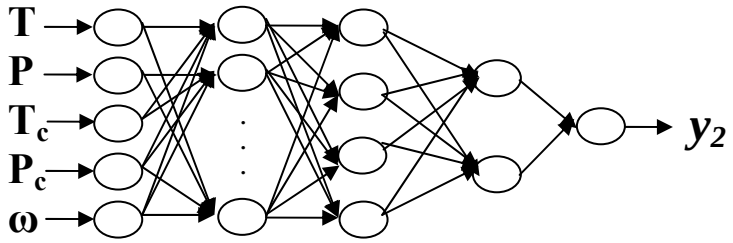

Figure 2: Multi-layer feedforward neural network for the prediction of the solubility of the solid drug in the SCF phase.

The application of ANN modeling of the solubility of the four NSAID in $csCO_2$ was performed using MATLAB® and the strategy proposed by Plumb et al.[9] as follows:

1. The experimental data should be divided into a training set, a test set (when attenuated training is adopted) and a validation set. Each data set should be well distributed throughout the model space.
2. Initially, the model should be trained using the default training algorithm and network architecture. The parameters of the equation of the best fit (the slope and the y intercept of the linear regression) or the goodness of fit (correlation coefficient, R^2) are determined for validation plots of the predicted versus the experimental properties of the validation data set. These parameters are used as a measure of the predictive ability of the model. Where the agreement vector values approach the ideal, i.e. [α=1 (slope), β=0 (y intercept), R^2=1], little improvement in predictive ability is to be expected. The ANN model with the best agreement vector is retained and the procedure is stopped.
3. Where the values of the parameters of the agreement vector vary greatly from the ideal and the model is poorly predictive, modification of the number of hidden layer neurons is then considered.
4. If model performance remains unsatisfactory a systematic investigation of the effect of varying both the training algorithm and network architecture is required.

All the input and output data were scaled so as to have a normal distribution with zero mean and unit standard deviation using the following scaling equation:

$$Scaled\ value = (Actual\ value - \mu)/\sigma \quad (1)$$

Where μ and σ: are the mean and standard deviations of the actual data respectively. The values of μ and σ for the input and output data, referred to in Table 1 and Table 2, are listed in Table 3.

Table 3: Constants used for scaling and de-scaling of the data

	T (K)	P (MPa)	T_c (K)	P_c (MPa)	ω	$log(y_2)$
μ	303.15	8.00	749.70	2.33	0.6710	-5.72125
σ	333.10	25.00	1090.70	2.584	0.9670	-2.16749

Table 4: Structure of the optimized artificial neural networks model.

Type of network	Training Algorithm	Input layer	Hidden layers		Output layer	
		No. of neurons	No. of neurons	Activation function	No. of neurones	Activation function
FFBP NN	BRBP using Levenberg-Marquardt optimisation.	5	12	Logarithm sigmoid	1	Linear
			4	Logarithm sigmoid		
			2	Logarithm sigmoid		

RESULTS AND DISCUSSION

The predictive ability assessment requires evaluation of data records excluded from the training set. Accordingly, the validation agreement vector and the validation agreement plot of the predicted versus the experimental outputs for the validation data set were used to evaluate the predictive ability of the NN model. The plot and the parameters of the linear regression are, straightforwardly, obtained using ***postreg*** MATLAB function. Figure 2 shows the validation agreement plot for the natural logarithm of the solubility with an agreement vector approaching the ideal, [α, β, R^2] = [0.983, -0.0619, 0.996]. Table 5 shows the validation agreement vector and the commonly used deviations, calculated per binary for the training and validation data sets:

- Average Absolute Relative Deviation:

$$AARDy_2(\%) = \frac{100}{N}\sum_{i=1}^{N}\left|\frac{y_2^{\exp} - y_2^{cal}}{y_2^{\exp}}\right|_i \qquad (2)$$

- Average Absolute Deviation:

$$AADy_1(\%) = \frac{1}{N}\sum_{i=1}^{N}\left|y_2^{\exp} - y_2^{cal}\right|_i \qquad (3)$$

- Root Mean Square Error (square root of the average sum of squares):

$$RMSEy_2 = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(y_2^{\exp} - y_{21}^{cal}\right)_i^2} \qquad (4)$$

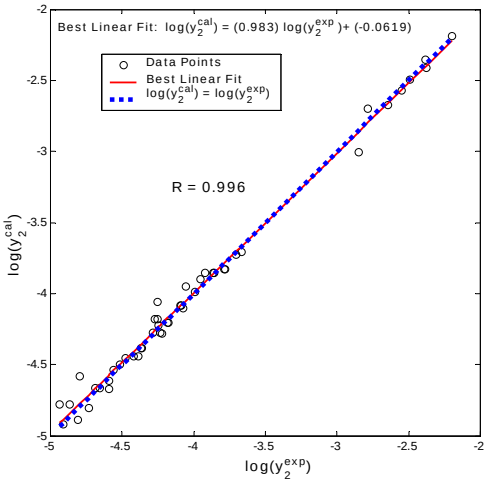

Figure 2: Validation agreement plot of the most predictive model of the solubility

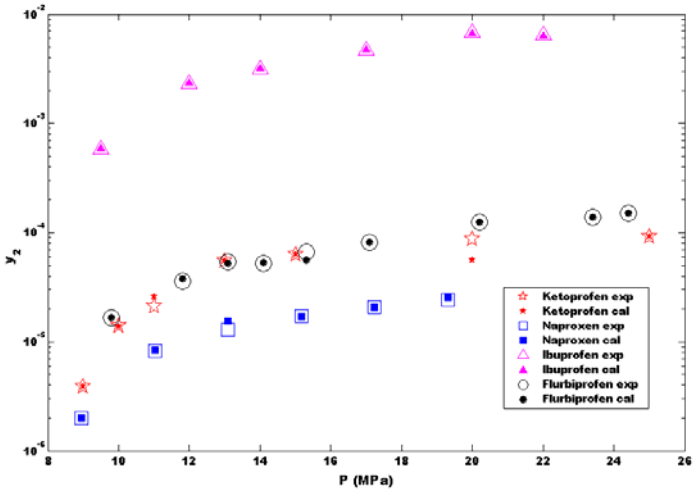

Figure 3: Experimental[5,6,7,8] and NN predicted solubility results for the four systems at 313 K.

The maximum of the Absolute Relative Deviation and the Absolute Deviation are those obtained for the solubility of Ibuprophen and are equal to 0.4207 and $0.4186.10^{-3}$ respectively.

Table 5: Statistical analyses of the error of the predicted results for the training and validation phases

	CO_2 (1) - Ketoprophen(2)	*CO_2 (1) - Naproxen(2)*	*CO_2 (1) - Ibuprophen (2)*	*CO_2 (1) - Flurbiprophen(2)* (SET1)	*CO_2 (1) - Flurbiprophen(2)* (SET2)	*CO_2 (1) - Flurbiprophen(2)* (SET3)
N	15	18	29	27	27	27
$AARDy_2(\%)$	5.7877	3.2799	4.7872	5.7248	2.7202	3.2715
$MaxARDy_2$	0.3615	0.2064	0.4207	0.3807	0.1575	0.1920
$AADy_2$ (%)	0.0004	0.0001	0.0093	0.0004	0.0002	0.0003
10^3.$MaxADy_2$	0.0317	0.0028	0.4186	0.0208	0.0161	0.0153
10^3.$RMSEy_2$	0.0087	0.0011	0.1448	0.0067	0.0043	0.0046
α y_2	0.9692	1.0117	1.0072	0.9657	0.9796	0.9836
10^4.β y_2	0.0363	-0.0044	-0.2737	0.0364	0.0128	0.0083
R^2 y_2	0.9886	0.9935	0.9972	0.9909	0.9963	0.9956

Figure 3 shows a semi log plot of the mole fraction solubility of the solid drug in $scCO_2$ (y_2) versus pressure at 313 K for the four systems. The figure shows an excellent agreement between experimental solubility (shown as white face markers) and NN predicted solubility (shown as dark face markers).

Tables 6-9 show a comparison between literature AARD(%) results, predicted by some cubic EoS, and those predicted by the ANN model of the present work. The deviations of the EoS predictions are very sensitive to the properties of the solid drug (critical properties, Pitzer's acentric factor and sublimation pressure) and can be very high as pointed out by Coimbra et al.[1]. The deviations of the ANN model prediction, however, are not sensitive to the critical properties and globally lower. Furthermore, the ANN model does not necessitate the knowledge of the sublimation pressure and the solid molar volume.

Table 6: Comparison between literature AARD(%) results predicted by some cubic EoS and the present work for the solubility of flurbiprophen

	T(K)	AARD(%) Set1	AARD(%) Set2	AARD(%) Set3
This work	303.15	2.32	1.81	1.84
	313.15	7.05	3.11	3.84
	323.15	9.37	3.64	4.79
Coimbra et al.[1]	303.15	6.61[a]	5.97[a]	5.49[b]
	313.15	15.01[a]	6.83[c]	5.16[a]
	323.15	12.24[c]	6.46[d]	3.25[d]

[a]PR EoS with vdW2 MR ; [b]SRK EoS with vdW2 MR;
[c]PTV EoS with MPR MR; [d]PTV EoS with vdW2 MR

Table 7: Comparison between literature AARD(%) results predicted by some cubic EoS and the present work for the solubility of naproxen

	T(K)	AARD(%)
This work	313.1	4.76
	323.1	1.37
	333.1	3.70
Coimbra et al.[1]	313.1	3.92[a]
Ting et al.[6]	323.1	13.2[b]
Ting et al.[6]	333.1	9.2[b]

[a]PR EoS with vdW2 MR ;
[b]SRK EoS with vdW1 MR ;

Table 8: Comparison between literature AARD(%) results predicted by some cubic EoS and the present work for the solubility of ibuprophen

	T(K)	AARD(%)
This work	308.15	5.57
	313.15	1.58
	328.15	5.72
Charoenchaitrakool et al.[7]	308.15	12.6[b]
Coimbra et al.[1]	313.15	4.21[a]
Charoenchaitrakool et al.[7]	318.15	32[b]

[a]PR EoS with vdW2 MR;
[b]PR EoS with vdW1 MR

Table 9: Comparison between literature AARD(%) results predicted by some cubic EoS and the present work for the solubility of ketoprophen

	T(K)	AARD(%)
This work	313 K	8.37
	328 K	3.53
Coimbra et al.[1]	313 K	8.30[a]

[a]SRK EoS with vdW2 MR ;

CONCLUSION

A feed forward artificial neural network model has been used to predict the solubility of four NSAID in $scCO_2$ given the equilibrium temperature, the equilibrium pressure and the critical temperature, the critical pressure and the acentric factor of the NSAID. The optimized NN consisted of five neurons in the input layer, three hidden layers with 14, 4 and 2 neurons respectively and one neuron in the output layer. This was obtained by applying a strategy based on assessing the parameters of the best fit of the validation agreement plots (slope and y intercept of the equation of the best fit and the correlation coefficient R^2) for the validation data set as a measure of the predictive ability of the model. The statistical analysis shows that the model was able to yield quite satisfactorily estimates. Furthermore, the deviation in the prediction of the solubility is comparable if not lower than that obtained by cubic EoS of PR, SRK and PTV combining van der Waals (vdW), Panagiotopoulos-Reid (PPR), and Mukhopadhyay–Rao (MPR) mixing rules. In contrast to EoS approach the ANN model does not rely on the sublimation pressure and the solid molar volume. Therefore, the ANN model can be reliably used to estimate the solubility of the four NSAID-$scCO_2$ binaries within the ranges of temperature and pressure considered in this work. This study also shows that ANN models could be

developed for the prediction of the solubility of a family NSAID in $scCO_2$, provided reliable experimental data are available, to be used in supercritical fluid processes. Hence, at least for a non expert in selecting appropriate EoS for the application in hand, alternatives to EoS are offered to be used in a more reliably and less cumbersome way.

NOMENCLATURE

AAD	Average Absolute Deviation	P	Equilibrium pressure (MPa)
AARD	Average Absolute Relative Deviation	P_c	Critical pressure (MPa)
ANN	Artificial Neural Networks	PPR	Panagiotopoulos Reid
BRBP	Bayesian Regularisation Back Propagation	PR	Peng Robinson
EoS	Equation Of State	PTV	Patel Teja Valderama
FFBP	Feed Forward Back Propagation	R^2	Correlation coefficient
MaxAD	Maximum of the Absolute Deviation	RMSE	Root Mean Square Error
MaxARD	Maximum of the Absolute Relative Deviation	SRK	Soave Redlich Kwong
MPR	Mukhopadhyay Rao	T	Equilibrium temperature (K)
MR	Mixing Rules	T_c	Critical Temperature (K)
N	Number of data points	vdW	Van der Waals
NN	Neural Networks	y	Mole fraction solubility
Greek letters			
μ	Mean	σ	Standard deviation
α	Slope of the linear regression equation	ω	Acentric factor
β	y intercept of the linear regression equation		
Subscripts		***Superscripts***	
1	Component 1	cal	calculated
2	Component 2	exp	experimental

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REFERENCES

[1] P. Coimbra, C.M.M. Duarte and H.C. de Sousa, *Fluid Phase Equil.*, **2006,** 139, 188-199.

[2] R Tabaraki, T. Khayamian, and A.A. Ensafi, *Dyes and Pigments* **2006** 73, 230-238.

[3] R Tabaraki, T. Khayamian, and A.A. Ensafi*, J. Molec. Graph. and Model.*, **2005**, 25, 46-54.

[4] C. Si-Moussa, S. Hanini, R. Derriche, M. Bouhedda, and A Bouzidi, *Braz. J. Chem. Engng*, **2008,** 25, xxx-xxx (in press).

[5] A. Stassi, R. Bettini, A. Gazzaniga, F. Giordano and A. Schiraldi, *J. Chem. Eng. Data* **2000,** *45,* 161-165.

[6] S.S.T. Ting, S.J. Macnaughton, D.L. Tomasko, and N.R. Foster, *Ind. Eng. Chem. Res.* **1993,***32***,** 1471-1481.

[7] M. Charoenchaitrakool, F. Dehghani, N.R. Foster and H.K, Chan, *Ind. Eng. Chem. Res.* **2000,** *39***,** 4794-4802.

[8] A.R.C. Duarte, P. Coimbra, H.C. de Sousa, and C.M.M. Duarte, *J. Chem. Eng. Data* **2004,** *49,* 449-452.

[9] A.P. Plumb, R.C. Rowe, P. York, and M. Brown, *Eur. J. Pharm. Sci.* **2005,** 25, 395-405.