Supercritical solvent impregnation: A semiquantitative method for the evaluation of affinity between polymers and drugs

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A supercritical fluid can be used in substitution of the original organic solvent for the preparation of pharmaceutical forms. The steps involved in the preparation are essentially similar to those of the traditional preparation but in this case the final purification is not required. The interest in the supercritical fluid impregnation of polymeric materials stems from the opportunity to utilize high diffusivity, low surface tension and the ease of solvent recovery for the preparation of new polymeric materials.

The partition of organic compounds between a polymer and a supercritical fluid has been studied by different authors and, despite the low solubility of the organic compound in the supercritical phase, high concentrations in the polymeric phase is easily reached.

Most of the applications concern the preparation of drug delivery systems using polymers that are also in the glassy state. Despite the increased number of experimental data, the theoretical framework for the complete understanding and description of the process is still not satisfactory especially regarding the interactions between the polymeric drug and the polymers.

The use of linear free energy descriptors is proposed to extrapolate experimental information on polymer organic solvents interaction to the evaluation of the interactions with drugs. The method proposed is validated comparing the calculated results with experimental data of drug – polymer impregnation.

INTRODUCTION

In different technological applications embedded or coated particles are needed to increase performances. These composite materials can be used as controlled delivery devices to sustain release of fertilized nutrients in soil in the agriculture area, to regulate the amount or persistence of a pharmacologically active agent in the body in the biomedical area.

In the traditional systems when the active component alone is present in the formulation, the solubilisation is a linear process both in the case of very soluble or insoluble (this word is used in order to define a component with reduced solubility) additive. The only difference is the final concentration in the receiving compartment. This behavior can be modified and will be discussed for the insoluble and very soluble additives separately.

In the case of an insoluble additive the decrease of particle sizes enhances the solubility but the dissolution kinetic is not modified if the dissolution process is governed by the purely thermodynamic solubility alone. For that reason the small additive particles are normally dispersed in different matrices, solid or liquid. Suspensions, emulsions, or solid polymeric particles embedded with the additive are the practical systems that allow a modified kinetic release.

In the case of high soluble additives the dissolution is delayed entrapping the additive in a matrix.

The process for the production of a controlled delivery system can be performed either by adding the filler to the matrix formation mixture, or by sorption of the guest molecule in the

previous synthesized matrix (f. ex. by diffusion from a gas phase or liquid solution). Careful removal of the solvent used in the impregnation process is essential in order to obtain a product acceptable on the basis of the actual regulation on the residual solvent content.
These residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practice or other quality-based requirements. The concentrations allowed for these solvents, controlled by international safety regulations [1], are generally restricted to few p. p. m..
Supercritical fluids (SF) and particularly carbon dioxide can useful substitute the normally used solvents. The supercritical solvent impregnation technique (SSI) [2] is very simple in principle and the basic idea is to substitute the organic solvents of the traditional methods with the SF solvent.
The steps involved in the preparation are essentially similar to those of the traditional preparation but in this case the final purification is not required.
Impregnation processes can be classified on the base of the following criteria:

1. The solubility of the solute in the supercritical fluid
2. The modification of the solute inside the polymer matrix

Two different mechanisms are possible: the first involves deposition of a substance soluble in a supercritical fluid into the polymer matrix upon depressurization. Even a solute with low affinity for the polymer matrix can be trapped within a polymer matrix, but re-crystallized particles within the polymer matrix are formed without a molecularly dispersed formulation. A different mechanism utilizes the high partition coefficient of solute between the polymer and fluid phases due to a high affinity of the solute for the polymer matrices. This mechanism has tremendous potential for the supercritical fluid impregnation of drug molecules into polymers [3].
The studies on the partition of organic compounds between a polymer and a supercritical fluid [4, 5] show that, despite the low solubility of the organic compounds in the supercritical phase, high concentrations in the polymeric phase are easily reached.
Most of these studies regard the partition of low molecular weight compounds and the extrapolation of these results to the systems of interest in the pharmaceutical industry requires particular care. As a consequence in addition to the kinetic problems (diffusion in the polymer matrix) the thermodynamic description of the ternary systems, supercritical fluid, pharmaceutical and polymer, is essential.

THERMODYNAMIC OF SSI SYSTEMS

The simplest system of interest in the SSI processes is a ternary system drug – polymer – supercritical fluid. The problem is simplified by the fact that most of the thermodynamic models need only parameters that reflect binary interactions.
The three binaries drug – supercritical fluid, polymer – supercritical fluid and drug – polymer subsystems.
Since the drugs are normally in the solid state at the temperatures at which they are processed the characterization of the binary SF - pharmaceutical is normally obtained by the knowledge of the solubility of the drugs in the supercritical fluid. These solubilities can be expressed in the case of equilibrium between the solid and the supercritical phase by the following expression:

$$Y_2 = \frac{P_2^{sub}}{P\hat{\Phi}_2^{scf}} \exp\left[\frac{v_2^s}{RT}\left(P - P_2^{sub}\right)\right] \qquad (1)$$

where the subscript 2 refers to the drug; v_2^s and P_2^{sub} are the molar volume and the sublimation pressure of component 2. The fugacity coefficient of component 2, $\hat{\Phi}_2^{scf}$, is calculated by using a thermodynamic model.
Alternatively the solubility [6] can be expressed with reference to the subcooled liquid with the equation:

$$Y_2 = \frac{f_{20}^L(T,P)\exp\left[\int_{P_0}^{P}\frac{v_{20}^S - v_{20}^L}{RT}dP + \frac{\Delta h_2^f}{RT_2^f}(1-\frac{T_2^f}{T})\right]}{P\hat{\Phi}_2^{scf}} \qquad (2)$$

where f_{20}^L is the fugacity of the component 2 in the liquid state at the temperature of the systems and the triple point pressure (since the triple point pressure P_0 is normally very low this corresponds to the vapor pressure), Δh_2^f and T_2^f are the heat of fusion and the melting point of the component 2. It is possible to simplify the equation (2) without loss of accuracy by dropping the first addendum of the exponential term, since the difference between the solid and liquid molar volumes is usually negligible.
The expression (2) presents some advantages respect to the equation (1) since it refers to fusion properties easily measurable instead of sublimation pressure. In fact the values of sublimation pressure for pharmaceutical compounds are very low and generally beyond the possibility of the different experimental techniques. On the other hand, in the equation (2) only the heat of fusion, the melting temperature, and the fugacity of pure solute in the sub cooled liquid phase (which can be calculated by the same equation of state used for calculating the fugacity in the supercritical state) are needed.
For the calculation of the fugacity in the supercritical phase different cubic and non-cubic equations of state are used. Nevertheless independent of the equation of state used the calculation of the pure component parameters for the pharmaceutical compound is a not solved problem. Since pure component properties normally used for this determination, vapor pressure and volumetric properties, are not known often prediction methods are used. Unfortunately depending on the method used large differences in the parameters and as a consequence different fugacity coefficient values are obtained [7].
The solubility can be also calculated with an equation derived from equation (2) but using the activity coefficient approach for the fugacity in the supercritical phase:

$$Y_2 = \frac{\exp\left[\frac{\Delta h_2^f}{RT_2^f}\left(1-\frac{T_2^f}{T}\right)\right]}{\gamma_2} \qquad (3)$$

Where the first exponential addendum was dropped and γ_2 is the activity coefficient of the solute drug in the supercritical phase.
Although many progresses have been done in the field very few attempts were done for the prediction of the solubility of a drug in the supercritical fluid.
Considering the data published in the recent years it is possible to evidence that generally the solubility of a drug is generally very low specially if carbon dioxide is used as supercritical fluid. Due to the non polarity properties of carbon dioxide the solubility of drugs with

different polar functional groups is generally between $10^{-3} \div 10^{-4}$ mole fraction and very often lower than 10^{-5}. These very low values can constitute a severe obstacle for a wide application of the impregnation methods.
The thermodynamic description of systems supercritical fluid - polymer, is receiving much attention in these last years due to the peculiar properties of these systems. The behavior depends strongly on several parameters: the chemical nature of the polymer and its physical state (such as T_g, degree of crystallinity, degree of cross linking, and chemical structure), the properties of the pure supercritical fluid (molecular structure, critical point), the nature of the interactions between the SF and the polymer, and obviously the external temperature and pressure.
The modulations of the glassy state and the glass-to-rubber transition have attracted intensive research interest [8 - 12]. In the last years polymer processing was the subject, of general reviews [13 - 16].
The sorption, the swelling and the glass transition depressions are generally modeled with Sanchez – Lacombe equation of state using at the glass transition temperature the Gibbs – DiMarzio criterion (the entropy of the mixture is zero in these conditions) [17].
Significant improvements [6] are obtained by accounting for the non random distribution of free volume and for highly specific forces, like hydrogen bonding, between neighboring molecules [18 - 20] and using a new combinatorial term derived from Stavermann: the model is known as nonrandom hydrogen-bonding (NRHB) model [21].
Sorption and swelling for glassy polymers are also modelled with the SL EOS and the introduction of an order parameter, the polymer density, to take into account the non equilibrium state of the glassy polymer (NELF model) [9, 22].
On these binaries our knowledge is still in an infancy stage due to the intrinsic difficulty of these systems. At the temperatures generally considered the polymer is below the glass transition temperature and the drug is below the melting point. Some qualitative information can be obtained extrapolating data obtained at higher temperatures where the drug is a liquid if at the melting point the drug is stable. Otherwise data obtained with normal organic solvents can be used to evaluate the interactions between the functional groups of the drug and those of the polymer.

SOLVATION THEORY

Quantitative structure – property relationships (QSPR) and linear free energy relationships (LFER) have proved to be useful tool for the analysis of interactions in binary systems. These relationships involve the use of a number of parameters (descriptors) that describe the properties of the solute molecule and, for extension, the behavior of the solute molecule in solution. In the construction of a general method a large number of molecular descriptors for each compound can be used and successively this number is reduced typically around 5 – 10. One of the possible disadvantages of this type of relationships is that the "best" set of descriptors for the correlation of a given property is very unlikely to be the same as the best set for the correlation of another property. For this reason in order to avoid this disadvantage the best way to construct valid QSPR and LFER relationships it to use a small number of predetermined molecular descriptors and the same small set is used for the description of the different properties.
Kamlett and Taft [23, 24] were the first to shown that is possible to define a rather small number of descriptors that could be combined in a linear way for the correlation of solute properties.

Successively Abraham and coworkers [25 - 28] have developed a more rigorous set of solute descriptors:

- E is an excess molar refraction relative to that of an alkane of equivalent volume. It is obtained from refractive index for solutes that are liquid at 20 °C. For solids, the refractive index of the hypothetical liquid at 20 °C can be calculated, or E can be obtained by the summation of fragments or substructures [29, 30].
- S is the dipolarity / polarisability that can be obtained from gas liquid chromatographic measurements on polar stationaty phases or more generally from water / solvent partition.
- A and B are the overall or effective hydrogen bond acidity and basicity that are most easily obtained from water – solvent partitions.
- L is the solute gas - n-hexadecane partition coefficient at 298 K.
- V is the McGowan characteristic volume [31] that can be calculated from bond and atom contributions [25].

Two different equations are proposed for the modelling of a solvation property SP [32]:

$$\log SP = c + eE + sS + aA + bB + lL \quad (1)$$

$$\log SP = c + eE + sS + aA + bB + vV \quad (2)$$

The equation (1) is used for the description of transport processes involving transfer from the gas phase to a condensed phase. The equation (2) describes transport processes involving two or more solution, liquid, or solid phases.

The solute descriptors represent the solute effect on various solute-phase interactions; the regression coefficients *c, e, s, a, b, l* and *v* correspond to the complementary effect of the phase on these interactions. The coefficients can be regarded as system constants and, containing chemical information about the phase, characterize the phase.

The e coefficient shows the tendency of the phase to interact with solutes through π and n-electron pair and it is usually positive. The s coefficient represents the tendency to interact with dipolar / polarizable solutes. The a coefficient depends on the hydrogen bond basicity of the phase (acidic solutes will interact with a basic phases), and b coefficient is a measure of the hydrogen bond acidity of the phase. The l coefficient is a combination of dispersion forces (that make a positive contribution) and cavity term (that makes a negative contribution): in general the dispersion effect is predominant and as a consequence the term is often positive. In the case of gases and water it is negative and for that reason it can be regarded also as a measure of the hydrophobicity of the phase. The v coefficient is also a measure of the hydrophobicity of the phase.

The molecular Abraham's descriptors are essentially determined on the basis of different experimental data. These descriptors were compared with the set of, theoretically calculated, molecular descriptors of Klamt's COSMO-RS [33 - 38]. It was found that the two sets contain essentially the same chemical information but differently distributed [39].

The numerical values of these descriptors can be calculated on the basis of the molecular structure of the different organic solvents [40]. In Table 1 the numerical values of the descriptors for some drugs are reported.

The Abraham's descriptors were applied extensively to model octanol water partition coefficients, the partition from gas to water and from gas to physiologically saline, the solubility in organic solvents and the partition from blood/plasma /serum to brain [32, 41 - 43].

Drug	A	B	L	S	E	V
Nimesulide	4.300E-01	1.100E+00	1.146E+01	2.680E+00	2.930E+00	2.079E+00
Piroxicam	7.200E-01	2.120E+00	1.320E+01	3.120E+00	2.560E+00	2.250E+00
Taxol	9.000E-01	4.130E+00	2.960E+01	5.220E+00	4.050E+00	6.204E+00
Vincristine	5.400E-01	4.250E+00	2.986E+01	4.300E+00	4.590E+00	6.083E+00
Vinblastine	5.400E-01	4.010E+00	2.894E+01	3.720E+00	4.460E+00	6.067E+00
Beta - Carotene	0.000E+00	9.900E-01	1.828E+01	1.010E+00	1.880E+00	5.054E+00
Progesterone	0.000E+00	1.040E+00	1.204E+01	2.490E+00	1.560E+00	2.622E+00
Megesterol acetate	0.000E+00	1.460E+00	1.377E+01	2.890E+00	1.730E+00	3.076E+00
Carbamazepine	3.900E-01	9.200E-01	1.079E+01	2.060E+00	2.120E+00	1.811E+00
Atenolol	7.800E-01	1.850E+00	1.068E+01	1.970E+00	1.480E+00	2.176E+00
Acyclovir	8.200E-01	2.190E+00	9.436E+00	2.270E+00	1.900E+00	1.521E+00
Ketoprofen	4.100E-01	1.370E+00	1.417E+01	2.780E+00	2.370E+00	2.727E+00
Theophylline	5.700E-01	8.700E-01	9.757E+00	1.970E+00	1.560E+00	1.978E+00
Temazepan	1.700E-01	1.340E+00	1.123E+01	1.760E+00	2.240E+00	2.133E+00
Griseofulvine	0.000E+00	1.580E+00	1.178E+01	2.320E+00	1.860E+00	2.395E+00
Colesterol	3.100E-01	8.100E-01	1.409E+01	1.760E+00	1.360E+00	3.494E+00
Ibuprofen	5.700E-01	5.100E-01	7.248E+00	1.010E+00	7.800E-01	1.771E+00
Alpha-Tocopherol	3.100E-01	7.400E-01	1.493E+01	8.500E-01	1.140E+00	3.966E+00
Beta-Tocopheroo	5.000E-01	7.400E-01	1.446E+01	9.100E-01	1.120E+00	3.825E+00
Gamma-Tocopherol	5.000E-01	7.400E-01	1.446E+01	9.100E-01	1.120E+00	3.825E+00
Delta-Tocopherol	5.000E-01	7.400E-01	1.399E+01	9.700E-01	1.090E+00	3.684E+00
Alpha-Tocopherol acetate	0.000E+00	8.000E-01	1.569E+01	9.800E-01	1.000E+00	4.263E+00
Paracetamol	9.100E-01	9.300E-01	6.501E+00	1.660E+00	1.120E+00	1.172E+00
Simvastatin	3.100E-01	1.450E+00	1.448E+01	2.290E+00	1.350E+00	3.427E+00
Itraconazole	0.000E+00	2.950E+00	2.597E+01	4.540E+00	4.650E+00	4.999E+00
Hydrocortisone	7.300E-01	1.900E+00	1.328E+01	2.920E+00	2.040E+00	2.797E+00
Naproxen	5.700E-01	7.500E-01	8.627E+00	1.490E+00	1.540E+00	1.782E+00
Salicylamide	6.200E-01	6.100E-01	6.129E+00	1.570E+00	1.160E+00	1.032E+00
Acetaminophen	9.100E-01	9.300E-01	6.501E+00	1.660E+00	1.120E+00	1.724E+00
Propranolol	2.900E-01	1.360E+00	1.013E+01	1.440E+00	1.760E+00	2.148E+00
Ofloxacin	5.700E-01	2.050E+00	1.337E+01	2.580E+00	2.260E+00	2.504E+00
Fluvastatin	1.200E+00	1.460E+00	1.555E+01	2.480E+00	2.750E+00	3.130E+00
Atorvastatin	1.610E+00	2.070E+00	2.201E+01	3.710E+00	3.610E+00	4.275E+00
Lovastatin	3.100E-01	1.440E+00	1.420E+01	2.340E+00	1.380E+00	3.286E+00
Clozapine	1.800E-01	1.440E+00	1.216E+01	1.820E+00	2.460E+00	2.431E+00
Lamotrigine	4.500E-01	9.300E-01	9.440E+00	2.130E+00	2.400E+00	1.645E+00
Cefuroxime axetil	7.200E-01	3.260E+00	1.872E+01	3.970E+00	2.630E+00	3.364E+00
Paroxetine	1.300E-01	1.230E+00	1.162E+01	1.770E+00	1.790E+00	2.387E+00

Table 1: Numerical values of some drug descriptors [40].

APPLICATIONS TO SSI

The Abraham method can be used for the evaluation of the interactions in the different binary systems of interest in the impregnation processes.

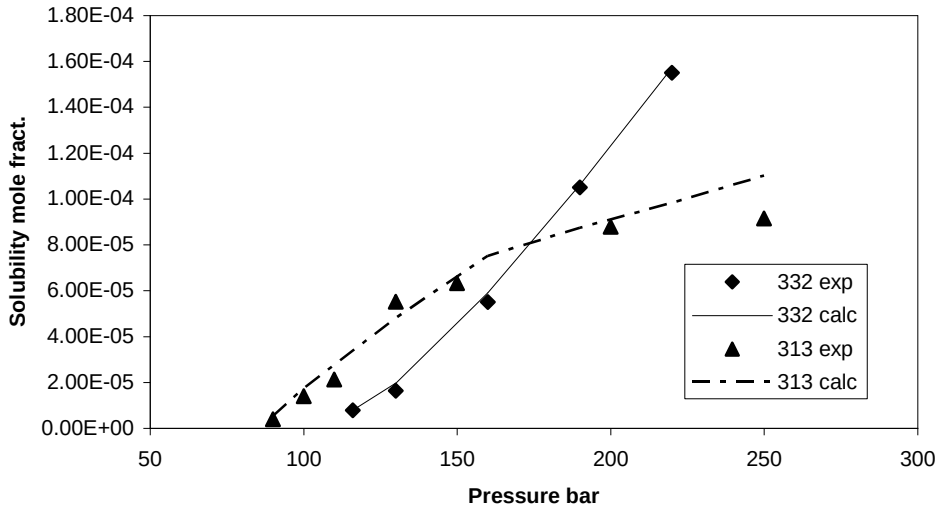

Figure 1: Application of solvation theory for the calculation of solubility of ketoprofen.

The evaluation and prediction of the solubility of drugs in supercritical fluids is a difficult task since also pure component properties needed are often missed. An attempt using the old version of solvation equation was proposed by Bush and Eckert [44]. They use the equation (3) assuming that, due to the low solubility in supercritical carbon dioxide, the activity coefficient is independent from concentration and is equal to the value at infinite dilution.

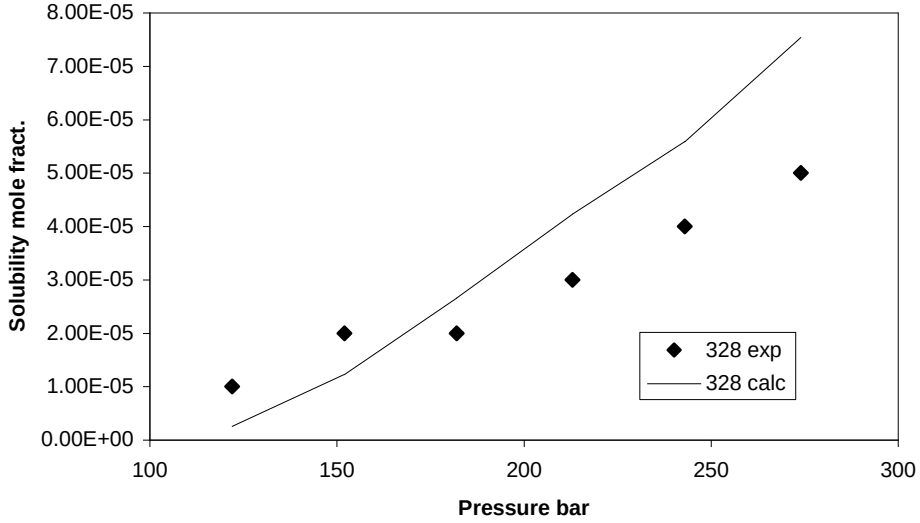

Figure 2: Application of solvation theory for the calculation of solubility of naproxen.

The activity coefficients were calculated from the experimental solubility data at 35°C and 289 bar and successively regressed using the solvation theory. Using empirical relations for the evaluation of the partial molar volumes and partial molar excess enthalpies it is possible to evaluate the solubility at different pressures and temperatures. In Figure 1 the excellent results obtained for the evaluation of the solubility of ketoprofen in carbon dioxide are reported.
In other cases the results are qualitative in the sense that the trend of variation of the solubility with pressure is correctly predicted but the estimated solubility values are not very close to the experimental data.
In literature applications of solvation theory for the characterization of polymer – organic solvent interactions are extensively reported [45 - 47]. In most cases the solvents are low molecular weight compounds and data regressed are obtained by gas – chromatography using the polymer as stationary phase [47]. In this way gas chromatographic retention volumes of the solvents are regressed and the specific solvation parameters of the polymers that are able to reproduce the partition are calculated. These parameters can be used for the prediction of the partition and, consequently, of the interactions between the polymer and other compounds provided that for these components the descriptors are known.

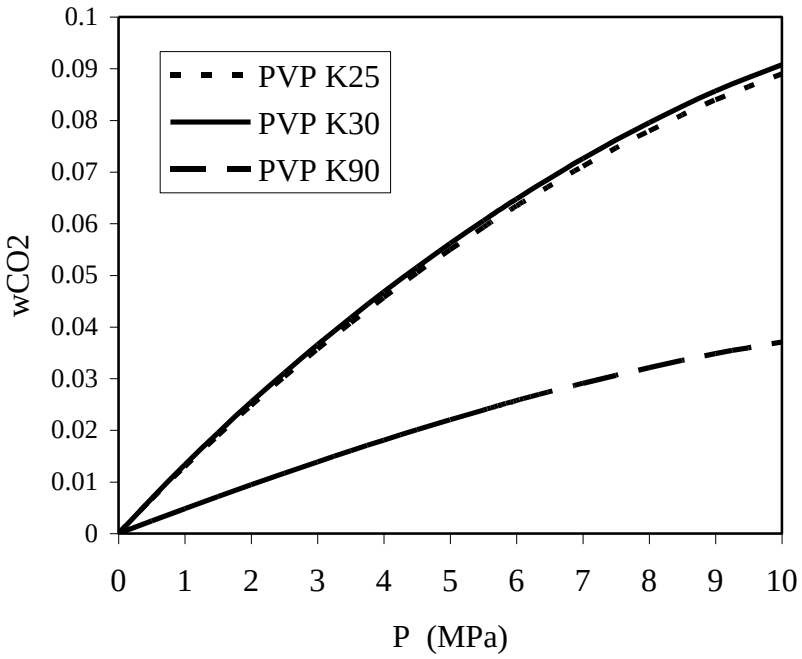

Figure 3: Prediction of sorption of carbon dioxide in PVP polymers.

The method was applied for the characterization of biocompatible polymers (until now more than 30 different polymers) [47 - 49] and for the evaluation of interactions between supercritical carbon dioxide and polymers and between drugs and polymers.
The fugacity coefficient of carbon dioxide at infinite dilution in the polymers is the basic information that is used for the calculation of the interaction coefficients of the Sanchez – Lacombe equation of state. Following the Condo approach [17] the sorption of supercritical

carbon dioxide in polyvinylpyrrolidone (PVP) polymers with different molecular weight is calculated and the data are reported in Figure 3.

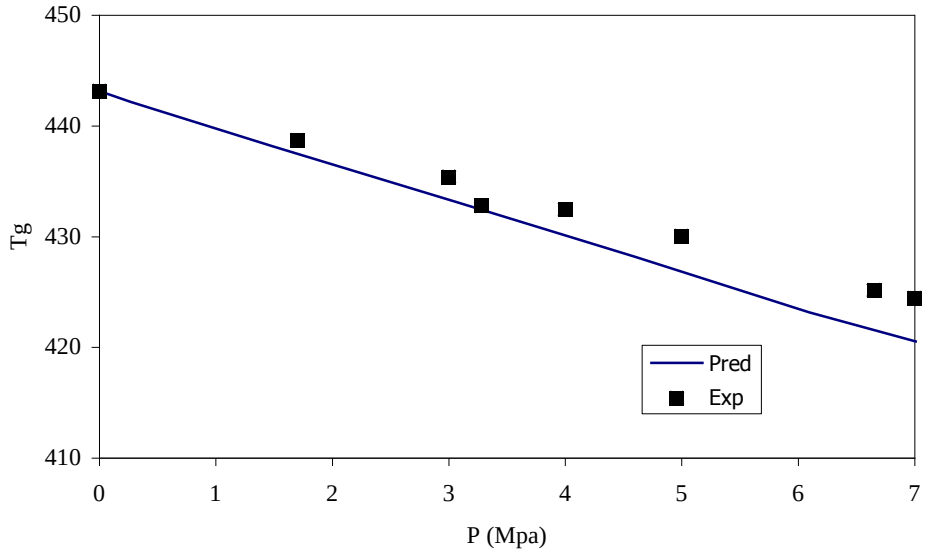

Figure 4: Experimental [50] and predicted glass temperature depression for PVP K 30.

Applying the Gibbs- Di Marzio criterium and on the basis of the binary interactions determined using the solvation theory the glass temperature depression determined by the supercritical carbon dioxide can be evaluated. In Figure 4 the results obtained for PVP K30 are reported and compared with the experimental data measured by Tomasko et al. [50]. The agreement is quite good and the differences increase at the higher pressures. These deviations can be explained by the fact that the characterization of the interaction between carbon dioxide and polymers are obtained at normal pressures and the values are subsequently extended to the higher pressures.

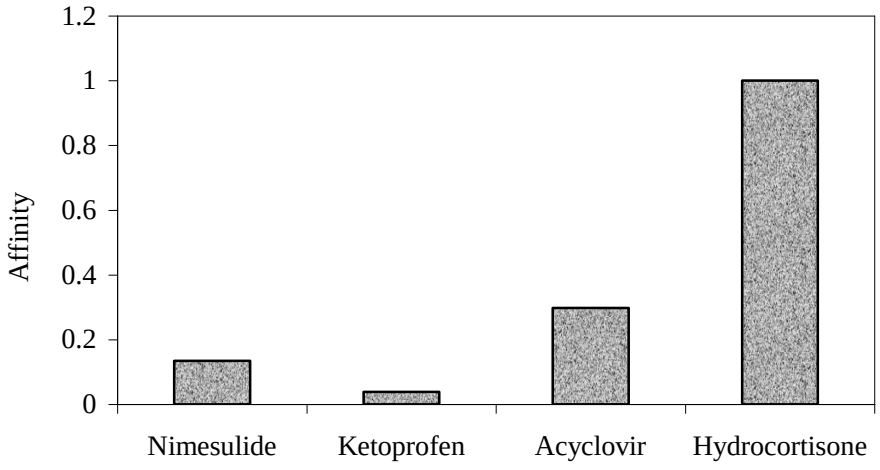

Figure 5: Affinity between drugs and PVP K30.

The third binary subsystem of interest in the impregnation processes is the binary system drug polymer. Due to the nature of these systems quantitative information on the interactions are limited. A semi quantitative evaluation of the compatibility between polymers and drugs can be derived from impregnation results. Unfortunately the application of the impregnation technique from the literature [51 - 54] frequently report data regarding one drug and one polymer and no comparison on the results obtained using the technique with different compounds is reported.
The solvation theory can be used for the determination of the interactions in these systems. In particular the fugacity coefficients of drugs in the polymer were calculated and the affinity was defined as the ratio between the fugacity coefficients of the different drugs. With this procedure it was possible to evaluate the affinity between piroxycam and different PVP polymers [55]. It was confirmed the experimental evidence [53] that it is easier to impregnate PVP K25 than PVP K 90. The same approach was used for the evaluation of the affinity of different drugs and PVP K30 polymer. Figure 5 reports the results obtained. Also in this case the experimental impregnation results are confirmed.

CONCLUSIONS

Applications of Abraham's salvation theory for the evaluation of the interactions and compatibility between the different components involved in the supercritical impregnation processes are reported. For some binary interactions (supercritical carbon dioxide – drugs and supercritical carbon dioxide – polymers) quantitative information are obtained. Work is in progress for a better description of the binary systems polymer – drug and for a description of the whole complete system.

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