BIOCOMPATIBLE POLYMERS CHARACTERIZATION BY IGC

Paolo Alessi, Febe Vecchione, Ireneo D. Kikic and Barbara Lafuente Valverde.
Department of Chemical, Environmental and Raw Materials Engineering (DICAMP), University of Trieste, Piazzale Europa 1, Trieste, Italy

Abstract

The use of polymers in the modern pharmaceutical industry is quite wide and needs a lot of different information. One of the more recent applications is the impregnation of a polymeric system with a drug using as carrier a supercritical fluid. This process is based on dissolving the active principle in a supercritical fluid, the supercritical solvent swells and reduces the glass transition temperature (T_g) of the polymer and the solute splits between the solvent and the matrix itself. The process is feasible only if the impregnating agent is soluble in the supercritical fluid, if the polymer is swollen by the supercritical solvent and the partition coefficient is favourable to charge the matrix with enough active principle.

In order to overcome these limitations other technological approaches have been suggested. In the Supercritical AntiSolvent Precipitation (SAS) process the drug co precipitates with a polymer from a drug solution in which the antisolvent (the supercritical fluid) is added: a uniform dispersion of the drug in the polymer matrix is obtained.

Whatever process is used the compatibilities between the different components plays a predominant role. Inverse gas chromatography (IGC) can be employed for collecting information useful for the characterization of the polymers and for the investigation of the equilibria involved.

In the IGC the obtained experimental data are the specific retention volumes V_g^0 of a solute injected in the stationary phase (the polymer in this case) at different temperatures: the plot of the retention volume logarithm versus the reciprocal of the temperature is called retention diagram from which it is possible to observe the plasticization and the phase transitions of the polymer investigated. The experimentally determined specific retention volumes V_g^0 can be used to characterize the investigated stationary phases in terms of dipolarity/polarizability, hydrogen-bond, basicity/acidity and lipophilicity by means of the equation of solvation proposed by Abraham. Experimental values of fugacity coefficients can be determined and utilized in connection with an equation of state model to predict the behavior of the substances investigated in different solvents and in carbon dioxide at high pressure. This thermodynamic approach has been applied to polyvinylpyrrolidones (PVP) which are polymers widely used in pharmaceutical and chemical formulations, in cosmetics, in paper and textile processes since they are physically and chemically inert, to copolymers of glycolide, a dimer of glycolic acid, and lactide, a dimer of lactic acid, (PLGA) which have been utilised in the medical industry for numerous biological applications including polymeric drug delivery devices, synthetic bone scaffolding, and even dental prosthetic devices and finally to different Eudragit® polymers.

Introduction

An increasing number of new chemical entities emerging from pharmaceutical researches are poorly or very poorly water soluble. Therefore, there is a great interest to develop reliable, efficient, and scalable methods to increase the bioavailability of these poorly water-soluble compounds [1].

Particularly, biocompatible and biodegradable polymers are largely used in medical and pharmaceutical applications. For example, biologically active ingredients are encapsulated in a polymer matrix for a controlled release of the compound [2].

PVP is a polymer widely used in pharmaceutical and chemical formulations, in cosmetics, because of its biocompatibility and non-systemic toxicity. The excellent solubility in water and in other solvents used in pharmaceutical production is an advantage in almost all dosage forms, e. g. in wet granulation in tablet production, in oral solutions, syrups and drops, in injectables and topical solutions and in film coatings on tablets. The adhesive and binding power is particularly important in tabletting (wet granulation, dry granulation, direct compression). This property is also useful in film coatings and adhesive gels. The affinity to hydrophilic and hydrophobic surfaces is particularly useful in the hydrophilization of a wide range of substances, ranging from hydrophobic tablet cores – to permit sugar or film-coating, to medical plastics.

In solid dosage forms, the ability of PVP to form complexes is used to increase drugs bioavailability.

Copolymers of glycolide, a dimer of glycolic acid, and lactide, a dimer of lactic acid, (PLGA) have been utilised in the medical industry, beginning with biodegradable sutures that were first approved in the 1960s. Since that time PLGA has been tested for numerous biological applications including polymeric drug delivery devices, synthetic bone scaffolding, and even dental prosthetic devices. Since PLGA is used in biological applications, the solvents used to process these copolymers should be pharmacologically acceptable. [3]

The polymer polylactide (PLA) can exist in an optically active stereoregular form (L-PLA) and in an optically inactive racemic form (DL-PLA). L-PLA is found to be semicrystalline in nature due to the high regularity of its polymer chain while DL-PLA is an amorphous polymer because of irregularities in its polymer chain structure. Hence the use of DL-PLA is preferred over L-PLA as it enables more homogeneous dispersion of the drug in the polymer matrix. Polyglycolide (PGA) is highly crystalline because it lacks the methyl side groups of the PLA. Lactic acid is more hydrophobic than glycolic acid and hence lactide-rich PLGA copolymers are less hydrophilic, absorb less water, and subsequently degrade more slowly.

The mechanical strength, swelling behaviour, capacity to undergo hydrolysis and subsequently the biodegradation rate are directly influenced by the cristallinity of the PLGA polymer. The resultant cristallinity of the PLGA copolymer is dependent on the type and the molar ratio of the individual monomer components in the copolymer chain.

PLGA polymers containing 50:50 ratio of lactic and glycolic acids are hydrolyzed much faster than those containing higher proportion of either of the two monomers. PLGA prepared from L-PLA and PGA are crystalline copolymers while those from DL-PLA and PGA are amorphous in nature.

The T_g of the PLGA copolymers are above the physiological temperature of 37°C and hence they are glassy in nature [4].

Eudragit® is the trade name for copolymers derived from esters of acrylic and methacrylic acid, whose properties are determined by functional groups. Depending on the pH, these polymers act as polyelectrolyte which make them suitable for different purposes, from

gastric or intestinal soluble drug formulations to insoluble but swellable delivery forms, regulated by percentage of charged and non-ionized (ether) groups in the structure of these polymers. Some of them can be considered as polycations (Eudragit® type E, RL, RS, and NE) and the others as polyanions (Eudragit® types L and S). The first ones can have positively charged groups: dimethylamino groups in Eudragit® type E, or quaternary amino groups in Eudragit® RL, RS and NE. The second ones can have negatively charged groups: carboxylate groups in both types L and S.
Eudragit E100 is an acrylic resin with cationic characteristics. It is obtained from the copolymerization of the dimethylaminoethylmetacrilate with methacrylic acid. It is soluble in water, in the gastric fluids and in buffer solutions with a pH 2-5.
Eudragit® RL and RS are obtained introducing in the molecular structure the trimethylammonioethylchloride group. They are insoluble in water and gastric fluids, but due to their high permeability and swelling capacity the release of active principles is possible with diffusion mechanism, independent from pH value [5-7].

Inverse gas chromatography (IGC) [8] has been used for the characterization of polymers for the past two decades. The IGC technique utilizes conventional gas chromatography, with minor modifications, to measure the interaction between pure solute (in the mobile phase) and the stationary phase in terms of retention time of the solute. The term “solute” is used to represent the low molecular weight, volatile solvent that is usually injected onto the chromatographic column. Solute is dispersed in a mobile phase and the polymer is stationary in the column as liquid phase.

In this study an investigation of different biodegradable polymers will be performed by means of the IGC technique [9, 10] in order to characterize them and successively to foresee the interactions with different type of drugs to choose therefore the appropriate polymer for each type of drug.

1. Experimental materials and method

1.1 Materials

Linear polyvinylpyrrolidones (PVP) with different molecular weight, PVP K25 (Mw=29.000), PVP K30 (Mw=40.000), and PVP K90 (Mw=360.000), were supplied by BASF; poly(DL-lactide/glycolyde) (PLGA), with different lactide-glycolyde ratios, PLGA 5050 (average M_w: 50000-75000) and PLGA 8515 (average M_w: 50000-75000) with the corresponding pure polymers poly-DL lactide (DL-PLA) (average M_w: 75000-120000) and poly-L lactide (L-PLA) were supplied by Sigma Aldrich; Eudragit® (Eudragit® E100, Eudragit® RL and Eudragit® RS).were supplied by Degussa.

The solutes used were reagent-grade products obtained from Fluka and Sigma-Aldrich. CO_2 was obtained from SIAD with a purity of 99.98%. Molecular structures of the polymers investigated are presented in figures 1-5.

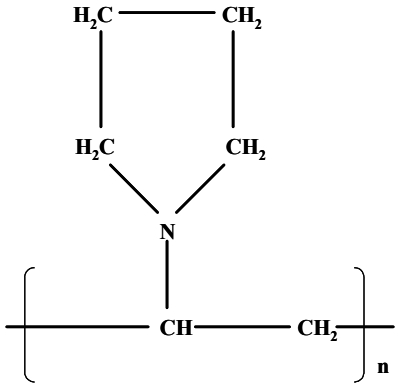


Fig. 1: PVP molecular structure.

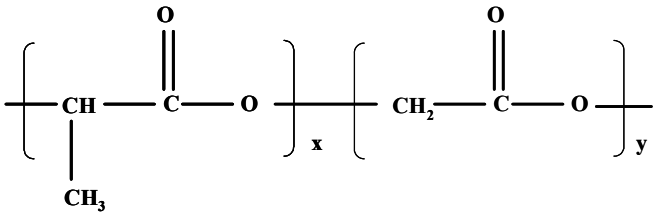


Fig. 2: PLGA molecular structure.

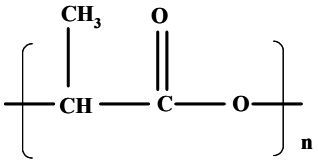
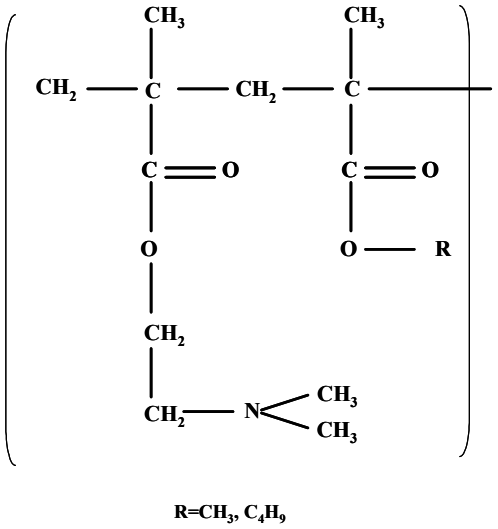


Fig. 3: L and DL-PLA molecular structure.



R=CH_3, C_4H_9

Fig. 4: Eudragit® E100 molecular structure.

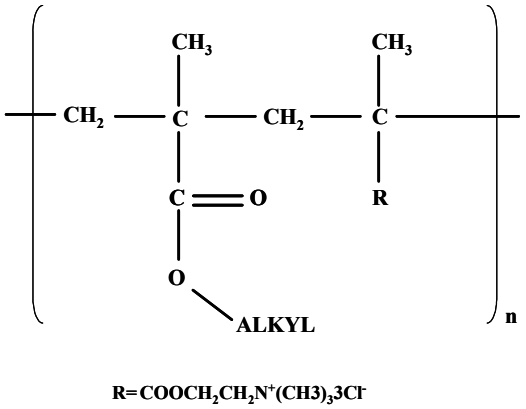


Fig. 5: Eudragit® RL/RS molecular structure.

1.2 Theory: study of polymer by IGC

The specific retention volume per gram of the polymer in the column, $V_g^{\,0}$, is determined experimentally during IGC experiments by the following relationship [11]:

$$V_g^{\,0} = \frac{Fm}{w} \cdot j \cdot \frac{p_O - p^{\,0}{}_{H_2O}}{760} \cdot \frac{273}{T_m} \cdot \left(t_R - t_a\right) \tag{1}$$

Where:

Fm = mobile phase flow;

w = stationary phase (polymer) weight;

p_O = outlet column pressure;

$p^{\,0}{}_{H_2O}$ = water vapor pressure at T_m;

T_m = flow meter temperature;

t_R = retention time;

t_a = inert retention time;

j = James – Martin factor which considers pressure drop in the chromatographic column, defined as:

$$j = \frac{3}{2} \cdot \frac{\left(p_i / p_O\right)^2 - 1}{\left(p_i / p_O\right)^3 - 1} \tag{2}$$

where p_i is the column inlet pressure.

From experimental retention volume $V_g^{\,0}$ is possible to calculate the weight fraction activity coefficient of the solute at infinite dilution, Ω_1^{∞}, which permits to evaluate the intramolecular interaction between the solute and the stationary phase.

Ω_1^{∞} are calculated with the following equation:

$$\ln \Omega_1^{\infty} = \ln\left(\frac{273.2 \cdot R}{V_g^{\,0} \cdot p_1^{\,0} \cdot M_1}\right) - \frac{p_1^{\,0} \cdot \left(B_{11} - V_1^{\,0}\right)}{RT} \tag{3}$$

Where p_1^0, M_1, V_1^0, and B_{11} are the saturated vapor pressure, the molecular weight, the molar volume and the second virial coefficient of pure solute.

Moreover, using the experimental V_g^0, fugacity coefficients at infinite dilution $\hat{\Phi}_i^\infty$ may be calculated by means of the following equation:

$$\hat{\Phi}_i^\infty = \frac{R \cdot T}{V_g^0 \cdot M_2 \cdot P} \tag{4}$$

where M2 is the molecular weight of the stationary phase and P the average pressure of the column.

1.3 Experimental apparatus

The experimental apparatus is presented in figure 6.

A Carlo Erba Chromatograph was used as GLC apparatus. The column temperature was controlled within ± 0.01°C and measured by means of a thermometer with thermocouple (Systemteknik AB S1220).

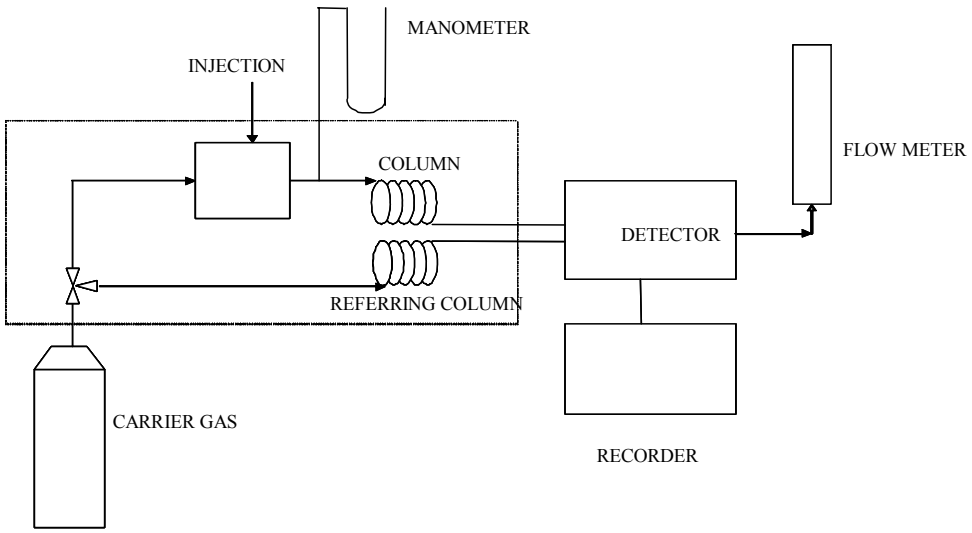


Fig. 6: Experimental apparatus adopted for IGC measurements.

The carrier gas (helium) flow rate was measured by means of a soap-film meter. The internal pressure gradient was measured to within ± 1 mmHg by a mercury manometer. The outlet pressure was atmospheric. The quantities of solutes injected were 0.1-0.3 μl. The operating conditions are summarized as follows: stainless-steel column (2 m long, 4 mm internal diameter); support: 100-120 mesh Chromosorb HP (Supelco); quantitative ratio of support to stationary phase = 4:1 (by weight), column pressure drop 500-530 mmHg [12].

2. Abraham method

Many theoretical approaches have been proposed in order to classify the stationary phases used in the gas liquid chromatography. Some of them are based on the use of chromatographic data relative to some reference substances to obtain characteristic parameter for stationary phase's characterization; others investigate the solute – solvent interactions adopting systems in which both stationary and mobile phase are characterized.

Abraham method [13-18] is based on the former criterion and utilizes a particular equation, the solvation equation, which allows obtaining a set of coefficients characteristic of the stationary phase from the chromatographic experimental data and from a set of characteristic parameters of the solutes injected.

The specific retention volume $V_g^{\ 0}$ can be considered as the result of partitioning equilibrium between solute molecules and the polymer.

Abraham et al. proposed the following solvation equation based on a simple cavity model of solvation:

$$\log V_g^{\ 0} = c + rR_2 + s\pi_2^{\ H} + a\alpha_2^{\ H} + b\beta_2^{\ H} + l\log L^{16} \quad (5)$$

Each term of this equation refers to some particular solute-solvent interaction. In particular there are five parameters which represent solute properties:

- R_2 a modified polarisability parameter that characterizes the ability of a solute to interact via □- or n-electron pairs;;
- $\pi_2^{\ H}$ solute dipolarity/polarisability parameter;
- $\alpha_2^{\ H}$ solute hydrogen – bond acidity;
- $\beta_2^{\ H}$ solute hydrogen – bond basicity;
- L^{16} Ostwald solubility coefficient of the solute on n-hexadecane at 298 K.

The constants c, r, s, a, b and l serve to characterize a solvent phase in terms of specific solute/solvent interactions; they are found by the method of multiple linear regression analysis (MLRA) from the experimental values of $\log V_g^{\ 0}$.

- c is a constant of the correlation;
- r: reflects the ability of a solute to interact with a solvent through π and n electron pairs;
- s: reflects the stationary phase polarizability;
- a: reflects interactions between hydrogen bond solute acids and a hydrogen bond solvent base (it's a measure of the stationary phase basicity);
- b: reflects interactions between hydrogen bond solute basics and a hydrogen bond solvent acid (it's a measure of the stationary phase acidity);
- l: reflects composite interactions and will include both an endoergic cavity term and an exoergic solute – solvent general dispersion interaction.

Normally b, a and s parameters are positive because, increasing solute – solvent interactions, gaseous solute solubility increases and therefore also $V_g^{\ 0}$ increases. Constant r is positive except for fluoridate stationary phases; finally, l parameter is generally positive due to the prevalence of the solute – solvent general dispersion interaction. In general a, b, l and s decrease increasing temperature.

The relative percentual error is expressed as follows:

$$\% = \left[\frac{\log V_g^{\,0}{}_{(pred)} - \log V_g^{\,0}{}_{(\exp)}}{\log V_g^{\,0}{}_{(\exp)}} \right] \quad (6)$$

3. Correlation of experimental data with the solvation equation

Parameters of solvation equation are reported for all the biocompatible polymers investigated in **tables 1-10**.

Table 1: Abraham's constants characterizing PVP K25.

T (K)	c	r	s	a	b	l	regression
493,27	-1,247	1,251	1,767	2,965	0,102	0,332	0.863
503,25	-1,227	1,170	1,646	2,728	0,082	0,320	0.857
513,22	-1,217	1,083	1,507	2,552	0,087	0,305	0.841
523,17	-1,152	0,987	1,354	2,284	0,116	0,275	0.823

Table 2: Abraham's constants characterizing PVP K30.

T (K)	c	r	s	a	b	l	regression
439,39	-1,425	1,366	1,687	2,892	0,204	0,385	0.836
503,36	-1,343	1,133	1,526	2,820	0,072	0,372	0.836
513,33	-1,166	0,953	1,337	2,648	-0,079	0,328	0.829

Table 3: Abraham's constants characterizing PVP K90.

T (K)	c	r	s	a	b	l	regression
503,05	-1,660	1,125	1,605	3,019	0,077	0,399	0.818
513,07	-1,533	0,969	1,507	2,873	-0,062	0,342	0.813
523,05	-1,578	0,980	1,524	2,801	-0,078	0,304	0.810

Table 4: Abraham's constants characterizing PLGA 5050.

T (K)	c	r	s	a	b	l	regression
352,4	-1,059	1,002	3,095	2,970	1,057	0,946	0.959
358,4	-1,050	0,993	2,938	2,794	1,078	0,901	0.960
373,4	-1,007	0,937	2,665	2,481	0,975	0,794	0.955
393,3	-1,056	0,852	2,374	2,212	0,813	0,706	0.955
413,3	-1,053	0,833	2,113	2,017	0,649	0,614	0.943

Table 5: Abraham's constants characterizing PLGA 8515.

T (K)	c	r	s	a	b	l	regression
353,4	-0,816	0,952	2,649	2,730	0,945	1,056	0.957
373,4	-0,976	0,867	2,481	2,513	0,719	0,934	0.953
393,3	-1,126	0,859	2,267	2,254	0,684	0,839	0.951
413,3	-1,219	0,844	2,107	2,090	0,584	0,757	0.955

Table 6: Abraham's constants characterizing DL-PLA.

T (K)	c	r	s	a	b	l	regression
353,15	-0,770	1,644	1,991	1,353	1,697	1,057	0.936
373,15	-1,725	1,801	1,936	1,501	1,904	1,120	0.911
393,15	-0,179	0,927	1,308	0,772	0,672	0,733	0.869
413,15	-1,136	0,946	1,851	1,396	0,714	0,785	0.963

Table 7: Abraham's constants characterizing L-PLA.

T (K)	c	r	s	a	b	l	regression
353,15	-2,256	1,264	2,474	3,484	1,673	1,288	0.907
373,15	-2,372	1,180	2,342	3,097	1,314	1,126	0.940
393,15	-2,895	1,055	2,565	2,859	0,958	1,071	0.948
413,15	-3,106	0,754	2,585	2,842	0,491	1,029	0.924
433,15	-2,497	1,291	2,007	2,350	1,067	0,928	0.859

Table 8: Abraham's constants characterizing Eudragit® E100.

T (K)	c	r	s	a	b	l	regression
363,15	-1,239	1,106	1,095	2,472	1,338	1,323	0,968
368,15	-1,237	0,999	1,173	2,398	1,185	1,284	0,972
373,15	-1,262	0,982	1,186	2,351	1,112	1,245	0,973

Table 9: Abraham's constants characterizing Eudragit® RL.

T (K)	c	r	s	a	b	l	regression
363,15	-1.143	0.558	2.532	6.294	0.396	1.215	0.994
368,15	-1.114	0.484	2.483	6.013	0.248	1.155	0.994
373,15	-1.175	0.472	2.451	5.700	0.247	1.139	0.993

Table 10: Abraham's constants characterizing Eudragit® RS.

T (K)	c	r	s	a	b	l	regression
363,15	-1.111	0.445	2.530	5.362	0.279	1.258	0.993
368,15	-1.055	0.449	2.431	5.046	0.217	1.178	0.994
373,15	-1.175	0.386	2.440	4.666	0.186	1.777	0.996

- For linear PVP a, r and s-constants are the predominant parameters. a-constant is greater than b for all the temperatures investigated denoting the basicity of all the PVP studied. In particular, a value is greater for PVP K90. The basicity (tendency of acid polymers to interact with hydrogen bond) is justified by the presence of nitrogen ion pairs in the polymer structure. s-constant value shows a high polarizability of the stationary phases investigated this can be justified with the presence of a ring in the PVP structure. s-constant is bigger for PVP K25 if compared to higher molecular weight PVP

  The tendency of stationary phase to interact with polarizable solutes, measured by the r-constant is lower for PVP K90.
- For PLGA a and s-constants are the predominant parameters.

  a-constant is greater than b for all the temperatures investigated denoting the basicity of the stationary phase. The difference between a and b-constants is more relevant for PLGA 8515.

  The basicity, measured by a-constant, decreases increasing temperature both for PLGA 5050 and PLGA 8515. It should be noticed that for temperature below 373.4K a is greater for PLGA 5050 while for temperature above 373.4K an opposite trend was found being a-constant predominant for PLGA 8515.

  s-constant value shows a high polarizability of the stationary phases investigated: it is bigger for PLGA 5050, it decreases with temperature and at 413.3K the values for both copolymers became close one to each other.

  The tendency of stationary phase to interact with polarizable solutes, measured by the r-constant is similar for all the copolymers studied and decreasing with temperature with greater values for PLGA 5050.

  Finally, l-constant, which is bigger for PLGA 8515, decreases with temperature for both the stationary phases.

  Therefore, it is evident that a change in the lactide-glycolyde ratio reflects on the polymers characteristics.
- For DL-PLA s and r-constant are the predominant parameters denoting dipole-dipole interactions. For L-PLA a and s-constant are predominant; moreover a is greater than b for all the temperatures investigated denonting the basicity of the stationary phase. It can be observed that the difference between a and b is greater for L-PLA while for DL-PLA they are quite similar from a numerical point of view.
- For Eudragit® E100 a and s-constant are the predominant parameter: a is slightly greater than b-constant denoting the basicity of the polymer. Eudragit® E100 shows a high polarizability because of the high s-constant value. For Eudragit® RL a, s and l-constant are predominant from a numerical point of view. The polymer shows a high basicity because of the great difference between a and b, while high value of s-constant

indicates a high polarizability of the polymer considered. The same considerations can be made for Eudragit® RS: although numerical values of s and l are quite the same for both polymers, a-constant is greater for Eudragit® RL. Therefore Eudragit® RL and Eudragit® RS have quite the same characteristics while there are some differences due to the presence and the quantity of trimethylammonioethylchloride groups, which influences the slightly higher values of r and l for Eudragit® RL.

Observing Abraham constants obtained for all the biopolymers investigated in this work, the following considerations can be made:

- The basicity (measured by a-constant) is bigger for Eudragit® RL and Eudragit® RS followed from those of L-PLA, linear PVP, PLGA, Eudragit® E100 and DL-PLA which is the less basic polymer investigated in this study.
- The polarizability (measured by s-constant) is bigger for PLGA 5050 and PLGA 8515. L-PLA, Eudragit ® RL and Eudragit® RS have quite the same value of s as PLGA 8515. The less polatizable polymers are DL-PLA, linear PVP and Eudragit® E100.
- The interactions with a solvent through π and n electron pairs (measured by the r-constant) are predominant for DL-PLA and linear PVP (which are similar to those of L-PLA). Lower values of r are obtained for both PLGA and for all the Eudragit® investigated in this study.

4. Modeling of experimental data: Sanchez and Lacombe theory

According to equation (4), from chromatographic experimental quantities is possible to calculate the fugacity coefficients at infinite dilution ($\hat{\Phi}_i^{\infty}$) of each solute (i) injected in the polymer. This approach permits the prediction of the solubility of the solute considered in the biopolymer.

Ethanol was chosen in this discussion, as example, because with methanol ethyl acetate and chloroform is one the most common solvent used for antisolvent precipitation technique, as reported in literature.

Figure 7 shows $\hat{\Phi}_i^{\infty}$ of ethanol behaviour as a function of temperature in linear PVP: it can be noticed the similarity of lower molecular weight PVP (PVP K25 and PVP K30) confirming the results obtained with Abraham method correlation. It is evident a higher solubility of ethanol in PVP K25 and PVP K30 if compared to that in PVP K90.

$\hat{\Phi}_i^{\infty}$ of ethanol in PLGA copolymers is presented in figure 8: in this case there is only a slight difference at a temperature below 375K, while at higher temperature ethanol solubility is similar in both copolymers.

The values of fugacity coefficients at infinite dilution can be calculated using the lattice fluid theory and the Sanchez-Lacombe equation of state, described elsewhere [19, 20].
In this study, as example, the calculation of fugacity coefficients at infinite dilution of CO_2 ($\hat{\Phi}_{CO_2}^{\infty}$) in the three PVP is reported.

The well-know lattice fluid equation state for the system is given by:

$$\tilde{\rho}^2 + \tilde{P} + \tilde{T}\left[\ln(1-\tilde{\rho}) + \left(1-\frac{1}{r}\right)\tilde{\rho}\right] = 0 \qquad (7)$$

$\tilde{T}$, $\tilde{P}$, and $\tilde{\rho}$ are the reduced temperature, pressure and density, respectively, defined as:

$$\widetilde{T} = \frac{T}{T^*};\ \widetilde{P} = \frac{P}{P^*};\ \widetilde{\rho} = \frac{\rho}{\rho^*} \tag{8}$$

T^*, P^*, and ρ^* are the three equation of state parameters defined by:

$$T^* = \frac{\varepsilon^*}{k};\ \ P^* = \frac{\varepsilon^*}{v^*};\ \ \rho^* = \frac{M_w}{rv^*} \tag{9}$$

where M_w is the molecular weight.

In the one-fluid approximation the average interaction energy per segment, ε^*, for a binary mixture constituted of component 1 and 2, is defined as follows:

$$\varepsilon^* = \Phi_1 \varepsilon_{11}{}^* + \Phi_2 \varepsilon_{22}{}^* - \Phi_1 \Phi_2 kTX_{12} \tag{10}$$

$$X_{12} = \left(\varepsilon_{11}{}^* + \varepsilon^*{}_{22} - 2\varepsilon_{12}{}^*\right)/kT \tag{11}$$

$$\varepsilon_{12}{}^* = \zeta_{12}\left(\varepsilon_{11}{}^* \varepsilon_{22}{}^*\right)^{1/2} \tag{12}$$

Φ_1 and Φ_2 are the segment fraction; $\varepsilon^*{}_{ii}$ is the interaction energy of component *i* that correspond to energy required for the creation of a vacancy in component *i*; ζ_{12} is the binary interaction parameter.

In the case of a binary mixture of a small molecule such as CO_2, (component 1) and a polymer (component 2) the chemical potential in the pure state of the solvent in the fluid phase is given by:

$$\frac{\mu_1{}^0}{kT} = r_1\left[\left(-\widetilde{\rho}_1 + \widetilde{P}_1\widetilde{v}_1\right)/\widetilde{T}_1 + \left(\widetilde{v}_1 - 1\right)\ln\left(1-\widetilde{\rho}_1\right) + \frac{\ln\widetilde{\rho}_1}{r_1}\right] \tag{13}$$

Equation 13 is obtained if the polymer doesn't dissolve in the solvent, therefore the fluid phase is constituted of the pure solvent.

The chemical potential of the component 1 in the mixture is given by:

$$\frac{\mu_1}{kT} = \ln\Phi_1 + \left(1 - \frac{r_1}{r_2}\right)\Phi_2 + r_1\widetilde{\rho}X_{12}\Phi_2{}^2 + r_1\left[\left(-\widetilde{\rho} + \widetilde{P}_1\widetilde{v}\right)/\widetilde{T}_1 + \left(\widetilde{v} - 1\right)\ln\left(1-\widetilde{\rho}\right) + \frac{\ln\widetilde{\rho}}{r_1}\right] \tag{14}$$

Equating equations 13 and 14 yields the equilibrium condition.

The model requires only one binary interaction parameter, $\square_{12}$, which denotes the strength of interaction between CO_2 and the biopolymer investigated.

With the Sanchez and Lacombe theory is possible to calculate the CO_2 fugacity coefficient, generally defined as:

$$\ln\varphi_i = -\ln z + r_i\left[-2\frac{\widetilde{\rho}}{\widetilde{T}} - \ln\left(1-\widetilde{\rho}\right)\right] + \left(\frac{z-1}{r}\right)\left[\frac{nr}{v^*}\left(\frac{\partial v^*}{\partial n_i}\right)_{n_j}\right] - \frac{\widetilde{\rho}}{\widetilde{T}}\left[\frac{nr}{\varepsilon^*}\left(\frac{\partial \varepsilon^*}{\partial n_i}\right)_{n_j}\right] \tag{15}$$

Where:

$$z = \frac{\widetilde{P}\widetilde{v}}{\widetilde{T}} r = r\left[-\frac{1}{\widetilde{\rho}} \ln(1-\widetilde{\rho}) - \left(1-\frac{1}{r}\right) - \frac{\widetilde{\rho}}{\widetilde{T}} \right] \tag{16}$$

and

$$\left[\frac{nr}{v^*} \left(\frac{\partial v^*}{\partial n_i} \right)_{n_j} \right] = \frac{1}{v^*} \left[r_i \left(-v^* + v_{ii}{}^* \right) \right]$$
$$\left[\frac{nr}{\varepsilon^*} \left(\frac{\partial \varepsilon^*}{\partial n_i} \right)_{n_j} \right] = \frac{1}{\varepsilon^*} \left[2r_i \left(-\varepsilon^* + \sum \Phi_j \varepsilon_{ij}{}^* \right) \right] \tag{17}$$

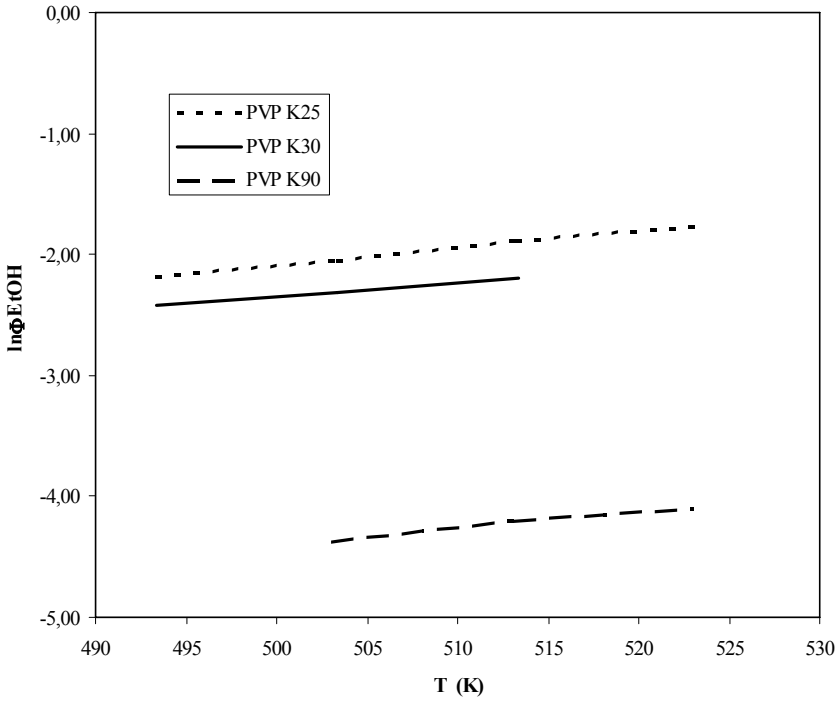


Figure 7: Fugacity coefficients at infinite dilution of ethanol in PVP.

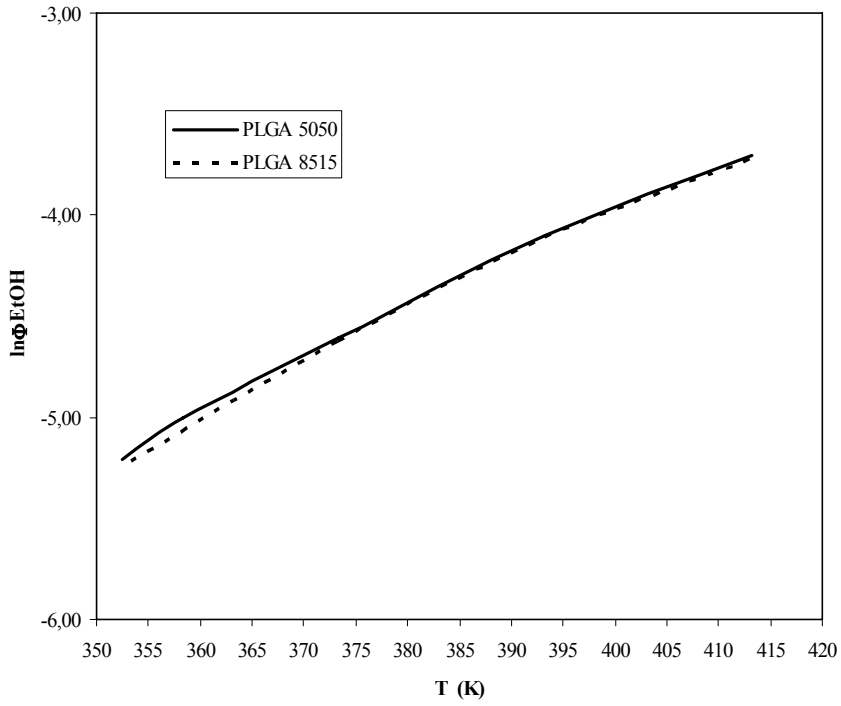


Figure 8: Fugacity coefficients at infinite dilution of ethanol in PLGA.

In Figure 9 the prediction of CO_2 sorption in the three PVP at 333 K is presented. Curves have been calculated with the following values of binary interaction parameter: 1.2245 for the binary system CO_2-PVP K25, 1.2260 for CO_2-PVP K30, and 1.1751 for CO_2-PVP K90. It is evident the higher affinity of PVP K25 and PVP K30 for CO_2, if compared to PVP K90. Also in this case PVP K25 and PVP K30 present a similar behaviour.

Figure 10 shows the T_g depression of the three PVP caused by CO_2 sorption. Also in this case it is evidenced the similarity between PVP K25 and PVP K30, whose curves are quite close one to each other. This behaviour confirms also sorption prediction: at a fixed pressure the T_g depression of PVP K25 and PVP K30 is greater than those of PVP K90 because of the higher quantity of CO_2 adsorbed. For PVP K25 and PVP K30 the model evidences the unusual phenomenon of the retrograde vitrification described elsewhere [20].

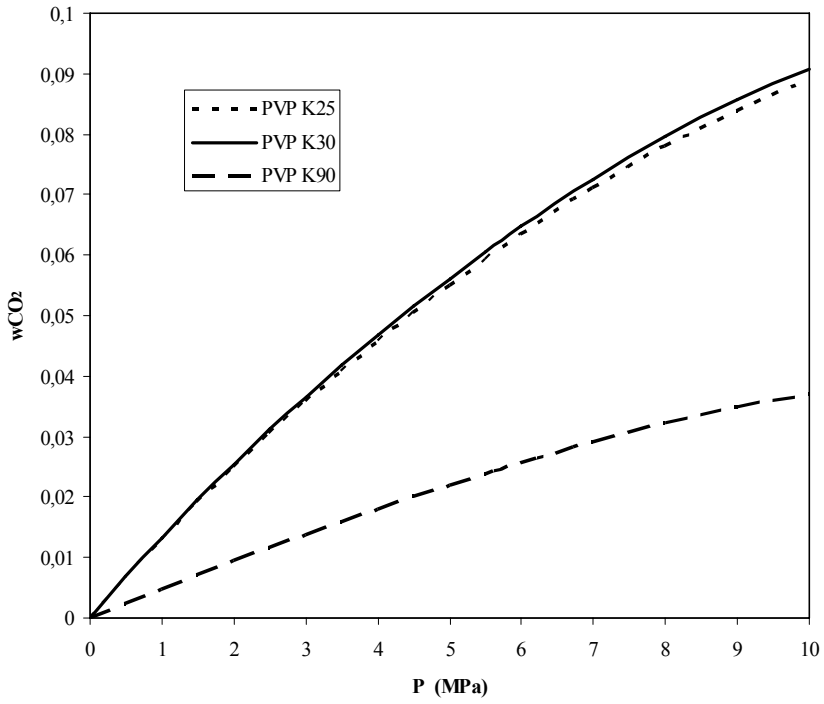


Figure 9: CO_2 sorption isotherms in PVP at 333 K.

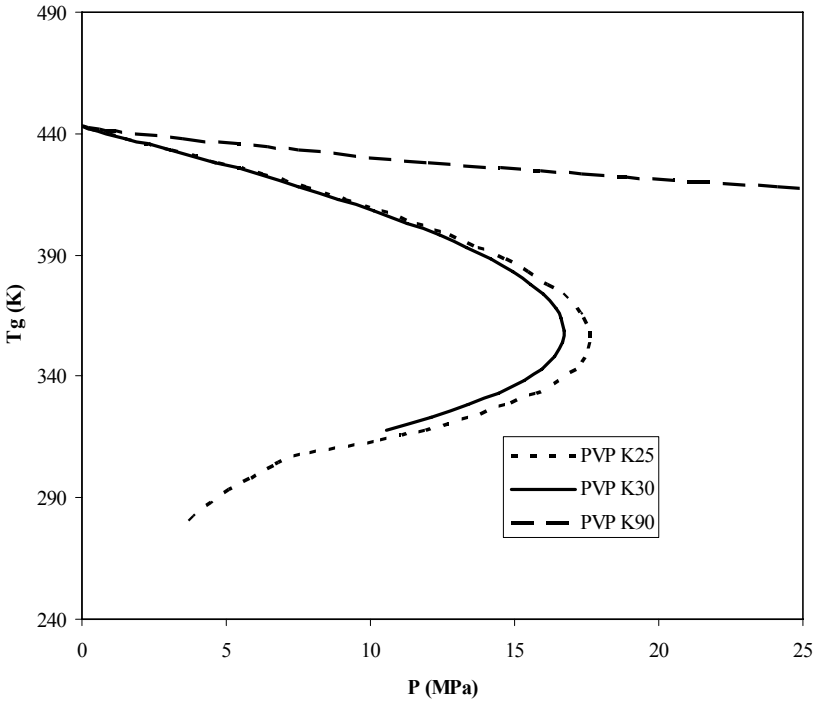


Figure 10: T_g behaviour as a function of the CO_2 pressure in PVP.

Conclusions

Different biodegradable polymers (three linear PVP with different molecular weight, two copolymers, poly(DL-lactide/glycolyde) (PLGA), with different lactide-glycolide ratios, two stereoisomers of poly lactide and three Eudragit) have been analyzed from a thermodynamic point of view with IGC technique. The retention data of 30 solutes were fitted with the Abraham salvation equation which allows the characterization of the polymers.

Abraham method successfully characterises all the biopolymers investigated evidencing the affinity and the differences between them.

Therefore, once known the active principle that has to be encapsulated in a polymer matrix, it will be possible to choose the appropriate biopolymers in terms of dipolarity/polarizability, hydrogen-bond, basicity/acidity and lipophilicity.

Finally Sanchez and Lacombe equation of state permits the calculation of infinite dilution fugacity coefficients of CO_2 in linear PVP. The model requires only a binary parameter which denotes the strength of interactions between CO_2 and the polymer.

With this parameter the prediction of CO_2 sorption at 333K and of the T_g depression in the mentioned biopolymers has been performed.

A high affinity of CO_2 for linear PVP with lower molecular weight (PVP K25 and PVP K30) was found; this causes a higher amount of CO_2 adsorbed and therefore a greater T_g depression.

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