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A semi-empirical model to simplify the synthesis of homogeneous and transparent cross-linked polymers and their application in the preparation of optical sensing films

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ABSTRACT

We propose a simple, semi-empirical model based on Hansen's solubility parameters for simplifying the synthesis and the optimization of homogeneous and transparent cross-linked polymers in order to obtain optical sensing films. More than 740 experiments were undertaken to demonstrate the reliability of the model and several applications are proposed. We have demonstrated that our model can help in the synthesis and optimization (percentage of cross-linker, changes in hydrophilicity, selection of porogens, quantity of template etc.) of homogeneous and transparent MIPs and NIPs (molecularly imprinted polymers) with VOCs; after the synthesis of 440 polymers in the homogeneity zone only 4.32% of them (19 samples out of 440) were heterogeneous. We suggest a role for its use in the development of novel polymeric resins for detecting volatile organic compounds in water by measuring intrinsic fluorescence, in simplifying the synthesis of imprinted polymers and in decreasing the number of experiments required to optimize optical sensing membranes. In addition, it might also be used for synthesizing and optimizing MIPs with a non-volatile template.

1. Introduction

Great emphasis is placed upon the value of homogeneous and transparent polymers as solid supports in sensing technology because both homogeneity and reproducibility of the chemical surface of the matrix has been shown to be crucial in the application of sensors. In addition, transparency is essential for sensing matrices intended for use in the development of optical sensing layers (Wolfbeis, 1991). Thus, several homogeneous and transparent polymers have been used to create optical sensing layers either by employing their intrinsic retention properties or by imprinting with a template molecule (Fernandez-Sanchez et al., 2009).

Molecular imprinting is a good way of achieving three-dimensional molecular recognition via the template-directed synthesis of highly cross-linked polymer matrices (Whitcombe and Vulfson, 2001). Molecularly imprinted polymers (MIPs) are attractive materials that allow the selective extraction of molecules from complex mixtures (Stevenson, 1999); It has become increasingly relied upon in many fields of chemistry and biology (Yan and Row, 2006) such as separative techniques (Ramström and Ansell, 1998; Armstrong et al., 1998; Spegel et al., 2003; Liu et al., 2006), competitive binding assays (Vlatakis et al., 1993; Chianella et al., 2002), catalysis (Ahmad and Davis, 1996; Davis et al., 1996), solid-phase microextraction (Koster et al., 2001; Hu et al., 2007; Djozan and Baheri, 2007; Tamayo et al., 2007; Turiel et al., 2007; Prasad et al., 2008) and biomimetic sensors (Dickert et al., 2000; Haupt and Mosbach, 2000; Avila et al., 2007; Salinas-Castillo et al., 2005; Sanchez-Barragan et al., 2005).

MIPs have the advantage of being physically robust, resistant to high temperatures and pressures and inert toward acids, bases, metal ions and organic solvents compared to Biomolecules (Sellergren and Lanza, 2000). These characteristics make MIPs one of the most suitable matrices in the development of chemical sensors instead of their biological counterparts (Kriz et al., 1997; Suedee et al., 2004; Yan and Row, 2006).

The disadvantages of these matrices compared to other state-of-the-art sensing layers include difficulties in their synthesis and their relative lack of sensitivity. Bearing in mind that the cross-linked gel must be homogeneous and transparent its synthesis is even more tedious because of the many variables to be taken into account (Yan and Row, 2006). As a result several works have been published using similar protocols to others previously described and many MIPs have been prepared by intuition and trial and error

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(Cederfur et al., 2003). Therefore it is somewhat difficult to find studies into the effect of the composition of MIPs and/or the kind and percentage of porogens to be used. Moreover, some researchers have tried to optimize the composition of the polymers by synthesizing and testing hundreds of MIPs to provide a library of MIPs for one analyte (Cederfur et al., 2003). These difficulties are increased considerably when the template is a volatile organic compound (VOC) due to its changing the medium in which the MIP is synthesized compared to a reference non-imprinted polymer (NIP) or altering the solubility of the medium in which polymerization is going to take place. For these reasons VOCs have been used very infrequently as templates (Yan and Row, 2006). Thus, we propose here a simple, semi-empirical model based on Hansen's solubility parameters to simplify the synthesis and optimization of homogeneous and transparent VOC-imprinted polymers.

2. Experimental

2.1. Chemicals

Methyl methacrylate (MMA), hydroxyethyl methacrylate (HEMA), ethylenglycol dimethacrylate (EDMA) and azobisisobutyronitrile (AIBN) were bought from Sigma–Aldrich and used as received. All the reagents were of analytical grade except for AIBN, which was of chemical purity grade, and all of them were used as received with no treatment before polymerization.

2.2. Synthesis of polymers

Six different polymers were used (polymer 1: 80% MMA–20% EDMA, polymer 2: 63% MMA–17% HEMA–20% EDMA, polymer 3: 46% MMA–34% HEMA–20% EDMA, polymer 4: 70% MMA–30% EDMA, polymer 5: 65% MMA–35% EDMA and polymer 6: 60% MMA–40% EDMA). All of them were synthesized following the same protocol (see electronic supporting information, ESI, Fig. ESI-1) but changing the ratio MMA–HEMA–EDMA and the kind and quantity of solvents.

2.3. Transparency of polymers

The transparency of the polymer was determined by observation, i.e. cross-linked gel must be produced as a simple phase and must be transparent; the apparition of more than 1 phase and/or opacity implies that it is heterogeneous or there is precipitation of particles during the polymerization and, therefore, it is not a polymer produce by solution polymerization.

3. Results and discussion

To develop and demonstrate the semi-empirical model we chose toluene as our VOC model. We selected a methacrylic polymer as cross-linked gel due to its versatility and applicability in imprinted polymers (Sellergren and Lanza, 2000). HEMA was added as a co-monomer to demonstrate that the semi-empirical model is also applicable to the co-polymerization of more than one monomer, since HEMA is widely used to increase further the hydrophilic characteristics of MMA cross-linked polymers.

As far as solvents (porogens) are concerned, these play an important role in the formation of the porous structure of MIPs. It is known that the nature and level of porogenic solvents determines the strength of non-covalent interactions and influences polymer morphology, which obviously exerts a direct affect upon the performance of the MIP (Yan and Row, 2006). First, the porogenic mixture should produce adequate porosity to assure good flow-through properties. Second, the porogens should have suitable polarity to reduce any interference during complex formation between the imprinting molecule and the monomers. Third, not only the reagents (template molecule, initiator, monomers and cross-linker) and products (dimers, trimers, . . .,) must be soluble in the porogens but also the cross-linked gel in formation must be swellable in the same porogen to afford a homogeneous and transparent MIP. In addition, for VOC-imprinted polymers the porogenic solvents are also responsible for the similarity between MIPs and NIPs; in our case, the MIP contains toluene whilst the NIP is toluene-free and thus the porogenic mixture must be chosen carefully in order to swell both the MIP and NIP during their polymerization to avoid the precipitation of the polymeric growing chains and to produce homogeneous, transparent and comparable polymers: both MIP and NIP must be obtained by solution polymerization.

3.1. Main conditions for obtaining homogeneous and transparent polymers

The homogeneity and transparency of the polymer depends mainly upon three parameters: the reactivity ratio between the monomers and cross-linker, the solvation properties of the mixture of porogens and the percentage of cross-linking.

The structure of the co-polymers can be established using the terminal model (Areizaga et al., 2002; Odian, 2004), which shows whether a co-polymer is statistical or not. To develop a chemically homogeneous polymer the mole fraction of a monomer within the polymeric structure must be approximately constant throughout the conversion process. ESI shows the change of degree of conversion versus the mole fraction of MMA–EDMA and MMA–HEMA (see Fig. ESI-2). It is possible to conclude that MMA, HEMA and EDMA have appropriate reactivity ratios to provide statistical polymers. On the other hand, during polymerization all the polymeric growing chains have to be solvated and therefore the Gibbs free energy of the solvated-chains to folded-chains process must be positive throughout polymerization. But if ΔG for the global process is positive, punctual folding during polymerization might occur. If this happens the polymeric growing chains fold because they are highly cross-linked and punctual folding is an irreversible process due to covalent bonds between the chains. Therefore, when ΔG for the global process is positive the result could be a folded polymer. This means that dG must be positive throughout the polymerization process in order to obtain a homogeneous and transparent polymer. ESI demonstrates that higher polymer-solvent interactions result in better solvation of the polymer throughout the polymerization process. Polymer-solvent interaction may be optimized by Hansen's solubility parameters for a mixture of solvents. Thus, we used these parameters to establish the semi-empirical model.

Finally, the third parameter, which controls the homogeneity and transparency of the polymer, is the percentage of cross-linking. An increase of the cross-linking results in an increase of the number of branches within the same polymeric growing chain and, therefore, in a reduction of the distance between polymeric chains. This increases polymer–polymer interactions and therefore decreases $|dG|$, which might lead to a negative dG and, therefore, punctual folding during polymerization

3.2. Relationship between Hansen's solubility parameters and the mole fraction in a mixture of solvents

The semi-empirical model is based on Hansen's solubility parameters for an ideal mixture of solvents (ESI shows how to get an ideal mixture of solvents). Hansen divided the solubility parameters into contributions for disperse (δ_d), dipole (δ_p) and hydrogen-bonding (δ_h) interactions (Hansen, 1967). In addition, it is possible to express the solubility parameters for a mixture of i

solvents as

$$\overline{\delta}_j = \sum_i \phi_i \delta_{i,j}; \quad j = \mathrm{d, p, h} \tag{1}$$

where $\overline{\delta}_j$ is the j solubility parameter of the mixture, Φ_i is the volume fraction of solvent i and $\delta_{i,j}$ is the solubility parameter, j, of solvent i (Barton, 1975). This expression may be applied for an ideal mixture of solvents with similar molar volumes.

To obtain a suitable $\overline{\delta}_j$ value for solubilizing both reactants (monomers, cross-linker, radical initiator etc.) and polymeric growing chains throughout polymerization, and bearing in mind that the MIP contains the template, which is a VOC (in our case toluene, which has low δ_h and δ_p) and the NIP is toluene-free, it is necessary to use at least two porogens: porogen b, which must have medium δ_h and δ_p values to counteract the absence of toluene in the NIP and porogen c, with high δ_h and δ_p to allow the solvation of the more polar chemicals. Therefore, the MIP can be considered as being a ternary mixture of solvents: template (solvent a) and two porogens (solvents b and c) and the NIP as a binary mixture of two porogens (solvents b and c). Thus, in the MIP $x_\mathrm{a} + x_\mathrm{b} + x_\mathrm{c} = 1$ and in the NIP $x_\mathrm{b} + x_\mathrm{c} = 1$, where x denotes mole fraction.

Finally, we propose the use of mole fraction instead of mole volume and thus the expression

$$\phi_i = \frac{n_i V^i}{\sum_k^3 (n_k V^k)} = \frac{x_i V^i}{\sum_k^3 (x_k V^k)} \tag{2}$$

where n is the number of moles, x is the mole fraction and V_i is the molar volume of solvent i for a mixture of 3 solvents (a, b and c) and so Eq. (1) becomes

$$\overline{\delta}_j = \frac{\delta_{a,j} x_a V^a + \delta_{b,j} x_b V^b + \delta_{c,j} x_c V^c}{x_a V^a + x_b V^b + x_c V^c}; \quad j = \mathrm{d, p, h} \tag{3}$$

Finally, on extracting x_c as a function of x_b, Eq. (3) becomes[1]

$$x_c = \frac{x_b [V^b(\delta_{b,i} - \overline{\delta}_j) + V^a(\overline{\delta}_j - \delta_{a,j})]}{V^c(\overline{\delta}_j - \delta_{c,j}) + V^a(\delta_{a,j} - \overline{\delta}_j)} + \frac{V^a(\delta_{a,j} - \overline{\delta}_j)}{V^c(\overline{\delta}_j - \delta_{c,j}) + V^a(\delta_{a,j} - \overline{\delta}_j)};$$

$$j = \mathrm{d, p, h} \tag{4}$$

Bearing in mind that the polymerization system is open and the solvents are evaporating throughout polymerization, the average values of the solubility parameter of the mixture ($\overline{\delta}_j$) and the mole fraction of the solvents are not constant. To simplify Eq. (4) we propose to use the initial values of both $\overline{\delta}_j$ and the mole fraction of the solvents. Thus, Eq. (4) becomes

$$x_c^0 = \frac{x_b^0 [V^b(\delta_{b,i} - \overline{\delta}_j^0) + V^a(\overline{\delta}_j^0 - \delta_{a,j})]}{V^c(\overline{\delta}_j^0 - \delta_{c,j}) + V^a(\delta_{a,j} - \overline{\delta_j^0})} + \frac{V^a(\delta_{a,j} - \overline{\delta}_j^0)}{V^c(\overline{\delta}_j^0 - \delta_{c,j}) + V^a(\delta_{a,j} - \overline{\delta_j^0})};$$

$$j = \mathrm{d, p, h} \tag{5}$$

where $\overline{\delta_j^0}$ is the solubility parameter of the mixture at $t = 0$ and x_b^0 and x_c^0 correspond to the initial mole fractions of solvents b and c respectively.

This expression is the basis of our semi-empirical model and shows how the initial mole fraction of solvents a, b and c must change to keep Hansen's solubility parameters constant in a ternary mixture. In addition, it helps us to find out whether a predetermined mixture of solvents can reach a determined Hansen's solubility parameter or not.

3.3. Establishment of the semi-empirical model

3.3.1. Establishing the limiting solubility parameters

The first step consists of synthesizing the polymer in each of the pure solvents a, b and c. These experiments reveal the limiting solubility parameters. For example, if a polymer is solvated by pure solvent c (the porogen with the highest δ_h and δ_p values), δ_h and δ_p are not limiting solubility parameters, δ_d alone must be considered for the establishment of the lower limit. If, on the other hand, the polymer is solvated by pure solvent a (the template with the highest δ_d) only δ_h and δ_p should be taken into account as limiting the upper limit. If the polymer is not well solvated by any of the pure solvents the three solubility parameters are limiting, which means that the system has both an upper and lower limit.

3.3.2. Establishing solubility parameter ranges in which the polymer is homogeneous and transparent

The second step consists of synthesizing the polymer in the presence of two solvents. The same protocol has been used in all the representations: the *Y*-axis corresponds to the binary mixture solvent a (template: low δ_h and δ_p) – solvent c (the most polar porogen), the *X*-axis corresponds to the binary mixture solvent a (template: low δ_h and δ_p) – solvent b (the less polar porogen) and the line $x_\mathrm{b} + x_\mathrm{c} = 1$ represents the NIP line ($x_\mathrm{a} = 0$: absence of template). Several windows of mole fraction for each binary mixture can be determined via these experiments. These windows correspond to windows of $\overline{\delta_j^0}$, i.e. a maximum and minimum value of $\overline{\delta_j^0}$, which can be obtained via Eq. (1) at $t = 0$ (see Fig. 1 for all the possibilities). If δ_d is the sole limiting solubility parameter (see Fig. 1a) each binary mixture has only a lower limit, which can be established by studying the a–c and a–b binary mixtures (see points 2 and 3 in Fig. 1a). If δ_h and δ_p are the limiting solubility parameters (see Fig. 1b) each binary mixture has only an upper limit. These upper limits can be established by studying the a–c and b–c binary mixtures (see points 1 and 4′ in Fig. 1b). When δ_h, δ_p and δ_d or δ_h and δ_d or δ_p and δ_d are the limiting solubility parameters, upper and lower limits appear for each binary mixture. Therefore, the three different binary mixtures (a–b, a–c and b–c) must be evaluated. Four different situations might occur (see Fig. 1c–f). Fig. 1a–c show the most common situations for a compatible polymeric system (statistical polymerization, well made selection of porogens and cross-linking lower than 25%). Fig. 1d and e are obtained when the choice of solvents is not the best; e.g. both δ_p values of solvents b and c are higher than δ_p of the polymer (see Fig. 1d) or both δ_p values of solvents b and c are lower than δ_p of the polymer (see Fig. 1e). Finally, Fig. 1f shows the results obtained when the percentage of the cross-linker is higher than 25%, in which case the polymer is not homogeneous and transparent when the a–c binary mixture is used. Therefore, a new point (5) has to be determined by studying the ternary mixture. This happens because an increase in the quantity of cross-linker requires a highly volatile solvent mixture since the volatilization of the porogens allows a faster interaction between the polymeric growing chains and hinders any interaction between the branches located in the same chain, which are responsible for the precipitation of the polymer. In our case, toluene, which has a high boiling point, is evaporated slowly and therefore the interaction between the polymeric growing chains decreases and the interaction between branches located in the same chain are encouraged. Thus it provides the precipitation of the polymer and not a transparent one. We surmise that the replacement of toluene with a more volatile solvent but with similar solubility parameters

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[1] Even when all the solubility parameters are affected by temperature, the use of their values at 25 °C is allowed in Eq. (4) for polymerization at a different temperature. This is explained and demonstrated in the ESI.

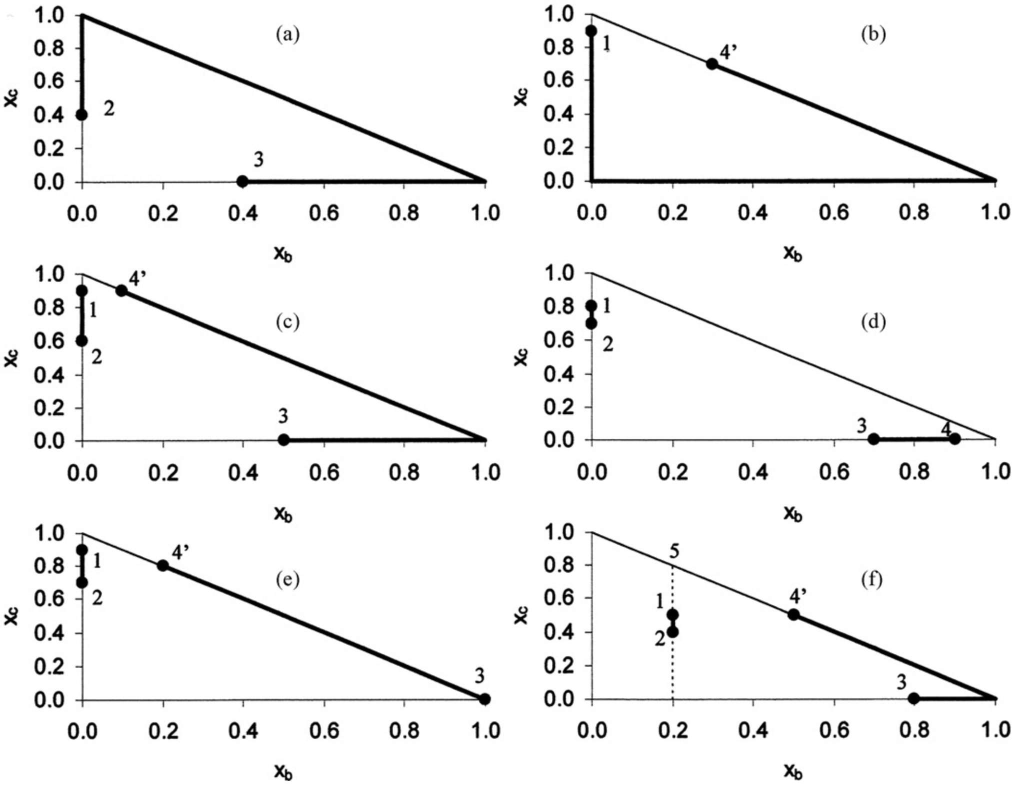

Fig. 1. Potential windows of mole fraction of binary mixtures in which the polymer is homogeneous and transparent (bold line). (a) Simulated polymer (not experimental data); (b) 80% MMA–20% EDMA, chloroform as solvent b and acetonitrile as solvent c; (c) 63% MMA–17% HEMA–20% EDMA, 1,4-dioxane as solvent b and acetonitrile as solvent c; (d) 63% MMA–17% HEMA–20% EDMA, acetone as solvent b and methanol as solvent c; (e) 46% MMA–34% HEMA–20% EDMA, chloroform as solvent b and methanol as solvent c; (f) 70% MMA–30% EDMA, chloroform as solvent b and acetonitrile as solvent c.

must provide a representation similar to that in Fig. 1c. Whatever the case, to achieve the main aim of this work the template has to have a much higher boiling point than those of the other solvents in order to avoid its evaporation and thus to allow the printing phenomenon.

As Fig. 1 shows, several windows of binary mixtures in which the polymer is homogeneous and transparent are always obtained (see the bold lines of each representation in Fig. 1). These windows of mole fractions are related to windows of $\overline{\delta_j^0}$ (maximum and minimum values), which are in turn related to δ_j of the monomers, δ_j of the polymeric growing chains, δ_j of the final cross-linked gel and the evaporation of the solvent during polymerization. Following this protocol we calculated the windows of mole fractions for the six polymers under study with different combinations of eight solvents: methanol, acetonitrile, acetone, chloroform, THF, 1,4-dioxane, CCl_4 and toluene (see ESI Tables ESI-1, ESI-2 and ESI-3).

3.3.3. Establishing the regions in which the polymer is homogeneous and transparent

The next step consists of extrapolating the results obtained for the binary mixture to a ternary mixture of solvents.

By using on the one hand the experimental maximum and minimum $\overline{\delta_j^0}$ values obtained in Section 3.3.2 and, on the other hand Eq. (5) it is possible to draw one line per point determined in the previous section. These lines determine the zone in which the polymer is homogeneous and transparent by taking into account only one of the solubility parameters. Therefore, three representations, one per solubility parameter, are obtained (see Fig. 2a and b) and three regions can be described in each representation: a white area, which corresponds to the values of x_a, x_b and x_c, in which the polymer is homogeneous and transparent (it corresponds with solution polymerization zone), a grey area, in which the polymer is heterogeneous (it corresponds with a mixtures of phases), and a black-dotted one, in which it is impossible to establish a priori whether the polymer is homogeneous or not. This zone is called the uncertain zone and is due to the differences between the boiling points of the solvents, as will be demonstrated later.

Each representation takes into account only one of the three solubility parameters. Therefore to obtain the region in which all three solubility parameters are taken into account simultaneously, the three representations have to be overlapped. This produces a similar figure containing the same areas: white, grey and black-dotted, but it takes into account all three solubility parameters (δ_p, δ_d and δ_h) at the same time (see Fig. 2c and d). To demonstrate that the white and grey areas correspond to homogeneous and heterogeneous polymers we applied Eq. (5) for polymers 1, 2 and 3 with several combinations of solvents. In all, 608 different combinations were assayed. All the polymers (289 samples) synthesized in the white area were homogeneous and transparent, and 98.53% (134 of 136 samples) of the polymers synthesized in the grey area were heterogeneous, whilst only 2 of the samples synthesized in the heterogeneous area were homogeneous and transparent. ESI (Fig. ESI-3) shows all the experiments carried out, which demonstrate the prediction capacity of the proposed semi-empirical method. On the other hand, 51.37% (94 of 183 samples) of the polymers synthesized in the uncertain zone (black-dotted area) were homogeneous and transparent and 48.63% (89 of 183) were heterogeneous. Thus the next step in verifying the semi-empirical model was devoted to studying this uncertain area.

3.3.4. Elimination of the uncertain zone

The uncertain zone appears because we are using $\overline{\delta_j^0}$ with an open system and solvents with different boiling points, and there-

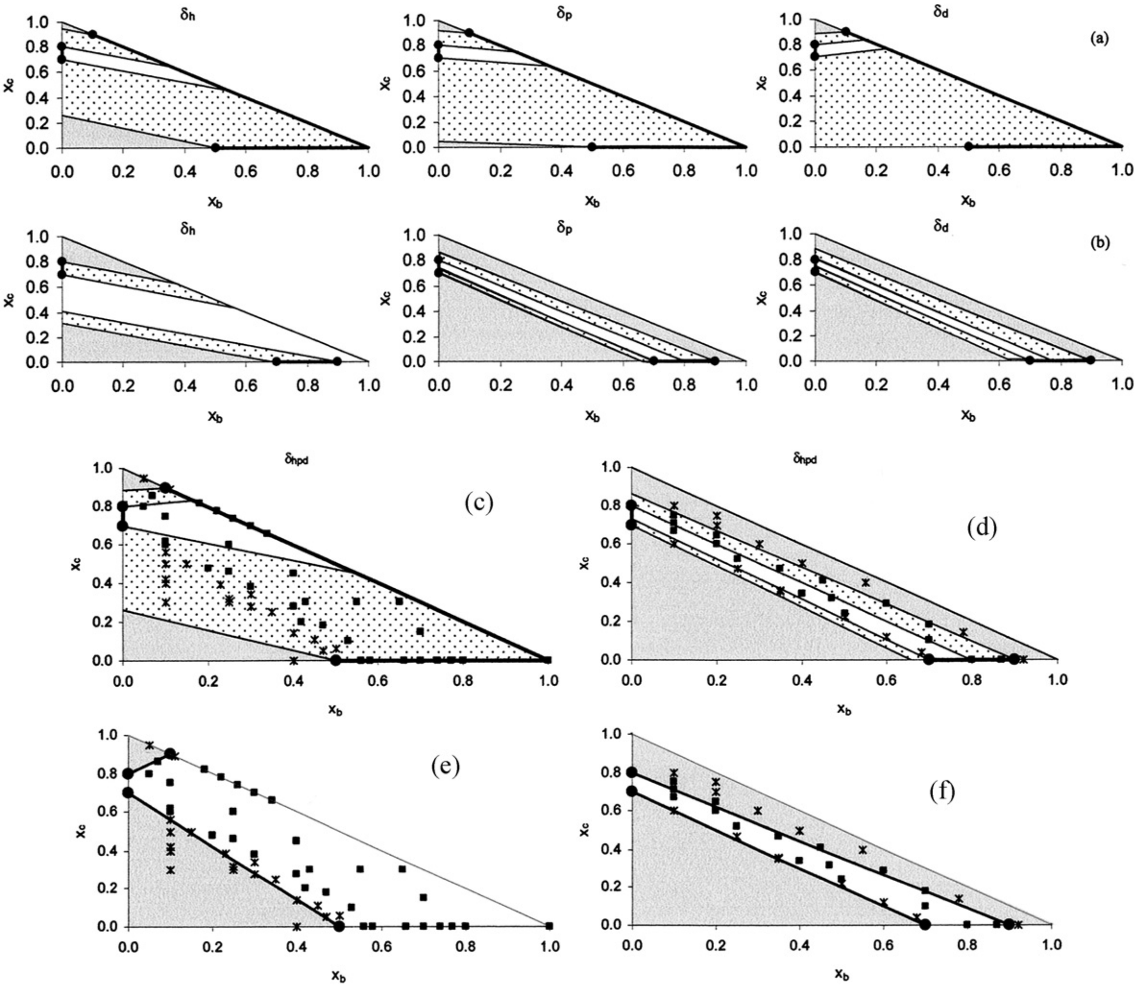

Fig. 2. Determination of the homogeneity (white), heterogeneity (light-grey) and undetermined (black-dotted) zones for the polymer 63% MMA–17% HEMA–20% EDMA taking into account only one of the solubility parameters when using the solvent mixtures: (a) toluene, 1,4-dioxane and methanol; (b) toluene, acetone and methanol; taking into account all three solubility parameters and using the solvent mixtures: (c) toluene, 1,4-dioxane and methanol; (d) toluene, acetone and methanol; and the elimination of the uncertain area: (e) toluene, 1,4-dioxane and methanol; (f) toluene, acetone and methanol. Symbol (■) is for homogenous experimental polymers and (✱) for heterogeneous and opaque ones.

fore, the solvents evaporate at different speeds. Thus, the changes in the value of $\overline{\delta_j^0}$ during polymerization depend upon the solvent mixture: the change in the value of $\overline{\delta_j^0}$ is not the same in the a-c axis as in the b-c axis. If the solvents have similar physical-chemical properties (such as their limiting solubility parameter, boiling point and molar volume) the deviation will be lower and the uncertain zone should decrease. In addition, the uncertain zone is also affected by any deviation from the ideal composition of the mixture of solvents.

To study the uncertain zone five polymers were prepared by using several combinations of solvents; similar results were obtained in all cases. Fig. 2c and d shows that for the x_a, x_b and x_c combination close to the axis (binary mixtures) the lines obtained via Eq. (5) fit the experimental results perfectly, but when this combination is at a distance from the axis Eq. (5) does not reveal whether a polymer is homogeneous and transparent or not. Therefore, ternary mixtures close to $x_b = 0$ respond in a similar way to an a-c binary mixture and combinations close to $x_c = 0$ are similar to an a–b mixture. From left to right, x_c decreases until $x_c = 0$ and x_b increases. Thus the steps are: a binary mixture a-c, then the ternary mixture a–b–c and finally the mixture a–b, bearing in mind that points 1 and 2 were obtained by evaluating the binary mixture a–c and points 3 and 4(4′) by using the mixture a–b. We may thus safely conclude that the transformation a–c to a–b–c to a–b occurs following the lines joining the points 1–4(4′) and 2–3 (see Fig. 2e and f), which shows that these lines describe the uncertain area perfectly.

ESI (Fig. ESI-4) shows all the experiments carried out. It can be seen that of the 742 polymers prepared (440 in the homogeneity and transparency zone and 302 in the heterogeneity zone) only 4.32% of them (19 samples out of 440) were heterogeneous in the zone of homogeneity and transparency and 2.65% (8 samples out of 302) were homogeneous and transparent in the heterogeneity zone. Therefore the uncertain area can be eliminated and Fig. 2c and d can be simplified as Fig. 2e and f, which shows only two regions, one in which the polymer is homogeneous and transparent (white zone) and another in which it is heterogeneous (grey zone).

An analysis of Figs. 2e, 2f and 3 reveals that it is possible to correlate the homogeneity/heterogeneity of the polymers with the solvation power of the solvent mixture throughout the polymerization process. Thus, if the solvent mixture is the most suitable, i.e. the combination of mole fraction is in the white area, it can solvate the polymer throughout polymerization and the resulting polymer is homogeneous and transparent (see Fig. 3B); it corresponds with a mixture of solvents which allows the solution polymerization. If the solvent mixture is at first favorable but at the

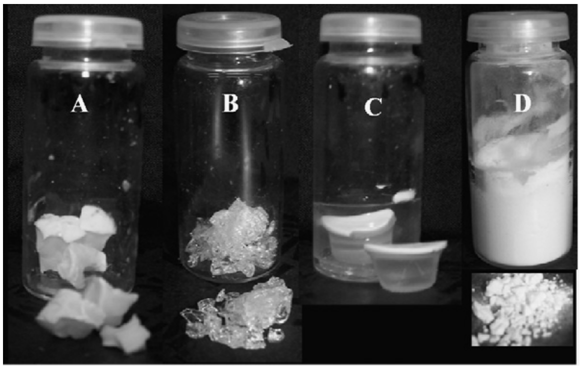

Fig. 3. Aspects of heterogeneous (A, C and D) and homogeneous and transparent (B) polymers. Composition: 63% MMA–17% HEMA–20% EDMA in (A) $x_{\text{toluene}} = 0.1$, $x_{\text{acetone}} = 0.2$ and $x_{\text{methanol}} = 0.7$, (B) $x_{\text{toluene}} = 0.2$, $x_{\text{acetone}} = 0.7$ and $x_{\text{methanol}} = 0.1$, (C) $x_{\text{toluene}} = 0.3$, $x_{\text{acetone}} = 0.1$ and $x_{\text{methanol}} = 0.6$ and (D) $x_{\text{toluene}} = 0.8$, $x_{\text{acetone}} = 0.1$ and $x_{\text{methanol}} = 0.1$.

end of polymerization cannot solvate it the resulting polymer has two phases, one transparent and other opaque, due to the folding of the polymeric growing chains at the end of the polymerization process; it corresponds with a heterogeneous mixture of phases. This phenomenon occurs close to the edge of the white area and the appearance of the polymer is similar to that shown in Fig. 3C. If the solvent mixture cannot solvate the polymeric growing chains during polymerization the resulting polymer is a powder (see Fig. 3D) containing particles of around 1 μm in diameter; it corresponds whit a mixture of solvent which allows the precipitation polymerization. This latter effect occurs with a x_a–x_b–x_c combination quite removed from the edge of the homogeneity zone. Finally, if the solvent mixture cannot solvate the polymer at the beginning of polymerization but evaporation of the solvent produces a mixture which can do so, the resulting polymer is an opaque bulk sample such as that shown in Fig. 3A, because first a powder is produced and then a crossliked gel adheres these particles; it corresponds again with a heterogeneous mixture of phases.

3.4. *How to apply the semi-empirical model*

We have demonstrated that the semi-empirical model can predict the solvent mixture in which the polymer will be obtained by solution polymerization and therefore it will be homogeneous and transparent. In this section we will summarize the procedure to obtain this area and to obtain Fig. 2e and f for other polymers.

The initial conditions which must be adhered to are:

1. The reaction conditions (temperature, pressure and total volume) must be chosen first because these parameters affect the region of homogeneity and transparency.
2. The solvents should be selected to provide an ideal mixture, or at least as ideal as possible (see ESI and Karger et al., 1978)
3. In addition, to produce a MIP the boiling point of the template must be significantly higher than those of the porogens in order to avoid any evaporation of the template and allow the printing of the polymeric matrix.
4. The monomers should be compatible; hence the reactivity ratio between the monomers and cross-linker is related to the formation of a statistical polymer, thus hindering the formation of chemically different polymeric chains and subsequent phase separation.

The steps for using the semi-empirical model are:

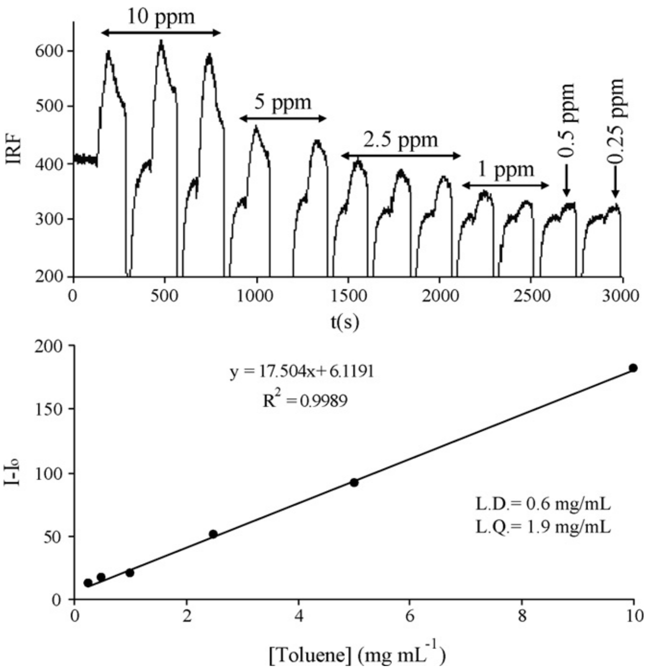

Fig. 4. FIAgram and sensor response (I–I_0) of the resins 20% EDMA–17% HEMA–63% MMA polymerized at 80 °C in a total volume of 7.4 mL of methanol ($x = 0.2$), acetone ($x = 0.68$) and toluene ($x = 0.12$) with various concentrations of toluene in water.

1. Selection of the polymerization conditions (temperature, pressure and total volume) and polymer composition (monomers, cross-linker, radical initiator and template).
2. Selection of the solvents due to be evaluated as porogens.
3. Synthesis of the polymer in the presence one by one of all the single selected porogens; for MIPs the template must be considered as being a component of the polymer composition and not as a porogen.
4. Evaluation of the binary mixtures in order to obtain points 1, 2, 3 and 4(4′), bearing in mind that for resins the solvents c, b and a must be chosen according with their polarity, where c is the most polar solvent and a is the least so; and for MIPs, solvent a is always the template and porogens c and b must be chosen according to their polarity, where c is the more polar solvent and b is less so.
5. Draw a line between points 1 and 4(4′) and points 2 and 3 and the region described by these two lines corresponds to the area in which the final polymer is homogeneous and transparent.

3.5. *Applicability of the proposed semi-empirical model*

The prime application of the proposed semi-empirical model is that of simplifying the synthetic process; it is possible to find out with only a few experiments the zones of x_a–x_b–x_c in which a polymer may be synthesized in a homogeneous and transparent form.

Apart from this, the main applications can be summarized as:

1. To prepare novel polymeric matrices that can be used as sensing films for optical applications due to an increase in and/or control of their porosity. Fig. 4 shows an example of a cross-linked gel that can be used as a sensing film for the detection of toluene in drinking water. Thus, the proposed semi-empirical model could simplify the study and optimization of novel resins.
2. To establish whether it is possible to synthesize both homogeneous and transparent MIPs and NIPs in order to make them comparable. Fig. 3A and B show pictures of heterogeneous and

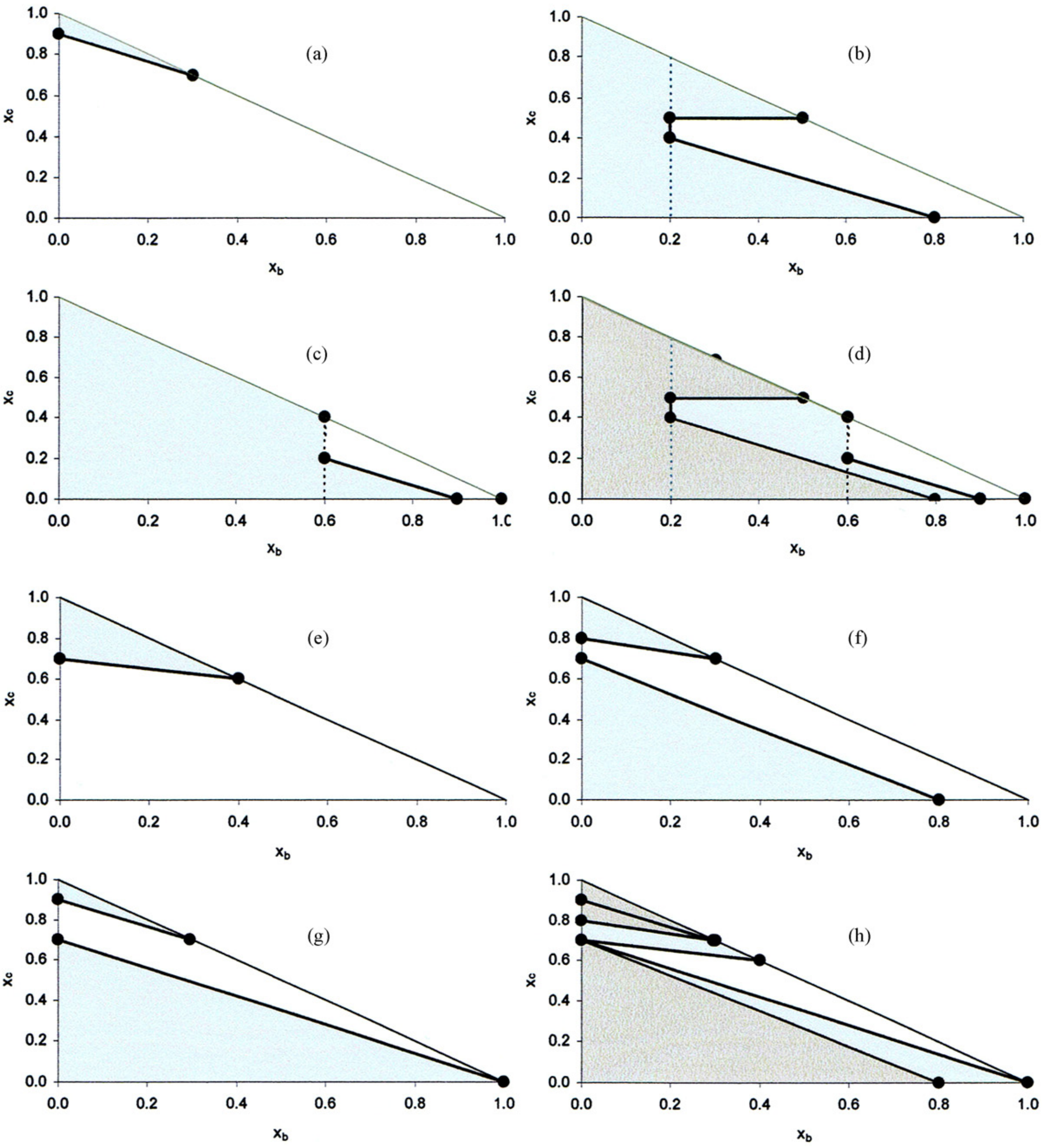

Fig. 5. Area of homogeneity of polymers containing different percentages of cross-linker for the ternary mixture toluene-CHCl$_3$-acetonitrile: (a) 80% MMA–20% EDMA, (b) 70% MMA–30% EDMA and (c) 65% MMA–35% EDMA and (d) the superimposition of the three diagrams; and containing different quantities of HEMA for the ternary mixture toluene–CHCl$_3$–methanol: (e) 80% MMA–20% EDMA, (f) 63% MMA–17% HEMA–20% EDMA and (g) 46% MMA–34% HEMA–20% EDMA and (h) the superimposition of the three diagrams.

homogeneous polymers synthesized under the same conditions but in the presence of different porogens. Whilst Fig. 3B is homogeneous and transparent Fig. 3A is heterogeneous and so they are incomparable. Fig. 2f shows that with the ternary mixture toluene (solvent a), acetone (solvent b) and methanol (solvent c) it is impossible to synthesize homogeneous and transparent MIPs and NIPs simultaneously because the area of homogeneity does not overlap the NIP line. If methanol is replaced by 1,4-dioxane, however, making the ternary mixture toluene (solvent a), 1,4-dioxane (solvent b) and acetone (solvent c), both MIPs and NIPs may be prepared by solution polymerization because the area of homogeneity overlaps that of the NIP (see Fig. 2c).

3. It also simplifies the selection of the x_a, x_b, x_c combination to produce homogeneous and transparent MIPs and NIPs, thus making it unnecessary to prepare them by intuition and trial and error.
4. It helps in the optimization process of MIPs and NIPs because all efforts can be focused upon the optimization of the polymers rather than their synthesis alone. For example, 30 experiments are enough to obtain the area of homogeneity and transparency of 3 polymers in which the percentages of the cross-linker are different (see Fig. 5a–d). They can be superimposed and a common x_a–x_b–x_c combination for all the percentage of EDMA can be selected in order to study how the percentage of cross-linker affects the analytical signal or the morphological or textural characteristics of the material.

Another similar example may be the optimization of the HEMA content to improve the hydrophilic nature of the matrix. Fig. 5e–h show the homogeneity and transparency areas of three polymers containing 0%, 17% and 32% HEMA. These can be superimposed and a common ternary diagram x_a–x_b–x_c combination for different HEMA composition selected in order to find out the effect of HEMA upon the penetrability and/or retention properties of the polymer.

The final example concerns the optimization of the porogens and/or template. All the previous experiments (Figs. 2e, 2f and 5) provide several combinations of x_a–x_b–x_c, which can be used to optimize the kind and concentration of porogens and/or template.

The proposed semi-empirical model can also be used to build ternary diagrams which facilitate the preparation of imprinted polymers with non-volatile templates. It is not always easy to find a good system for solubilizing all the components: template, monomers and cross-linker, and which allows the solution polymerization of the cocktail to obtain homogeneous and transparent matrices. Our model can also help in this task.

4. Conclusions

We propose a simple semi-empirical model based on Hansen's solubility parameters. The model simplifies the synthesis of homogeneous and transparent cross-linked gels (for use in optical measurement systems) and transforms it into a routine process, with the result that more effort can be directed towards studying the properties of materials rather than their mere synthesis. We have demonstrated that our model can help in the synthesis and optimization (percentage of cross-linker, changes in hydrophilicity, selection of porogens, quantity of template etc.) of homogeneous and transparent MIPs and NIPs with VOCs; after the synthesis of 440 polymers in the homogeneity zone only 4.32% of them (19 samples out of 440) were heterogeneous. In addition, the proposed semi-empirical model might also be used for synthesizing and optimizing MIPs with a non-volatile template: for example, (1) with templates with solubility parameters very different from those of the monomer's; (2) to evaluate the effect of porogens with substantially different solubility parameters; (3) to evaluate complex mixtures of monomers with different solubility parameters.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bios.2009.07.034.

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