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Partial solubility parameters of poly(D,L-lactide-co-glycolide)

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Abstract

During production of microparticles by the polymer incompatibility method a polymer solution is demixed. Therefore, investigations into solubility are often carried out when the suitability of a polymer is examined. Solubility parameters can be used to quantify the solubility. For polylactide and polyglycolide as commonly employed copolymers for microparticles the solubility parameters have rarely been documented. This study aimed to determine solubility parameters and partial solubility parameters for different proportions of lactide to glycolide for poly(D,L-lactide-co-glycolide) (PLGA). The employed methods were compared and solubility maps established. Finally the accuracy of the results was discussed for different polymer batches which were used for production of microparticles. Although the turbidity titration method was found to be the most precise, it was not possible to sufficiently explain the differences between three polymer batches during microparticle production.

Keywords: Poly(lactide-co-glycolide); Partial solubility parameter; Hansen parameter; Microparticle production

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1. Introduction

In the pharmaceutical industry, excipients and drugs are often characterized by solubility parameters. In connection with the production of microparticles, suitable solvents have been chosen for the solvent evaporation method, for example, Bodmeier and McGinity (1988) or Moldenhauer and Narin (1992, 1994). The production of microparticles by the polymer-incompatibility method is performed by demixing a polymer solution. Demixing is carried out using an incompatible polymer as the non-solvent, resulting in a phase rich in one polymer, present in the form of disperse droplets distributed in the continuous phase. The interaction between polymer and solvent influences the composition of the phases and thus also the properties of the microparticles which are produced. Routine production requires parameters by which the polymers, or their interaction with the solvent, can be quantified. To date, Hildebrand parameters or partial solubility parameters of poly(D,L-lactide) (PLA) or poly(D,L-lactide-co-glycolide) (PLGA) have

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seldom been published. Therefore, the aim in this study was to examine whether solubility parameters can be determined with sufficient accuracy by established methods. Three methods were applied: swelling method, turbidity titration method, and calculation using group contribution. Ultimately, the results should be compiled in a solubility map.

2. Materials and Methods

2.1. Swelling Experiments

Using the so-called solubility parameter, also referred to as Hildebrand parameter, instead of the root of cohesive energy density, the mixing enthalpy H_m can be written as Eq. (1); where V_1 denotes the volume of the solvent 1, φ_1 the volume fraction of the solvent 1, φ_2 the volume fraction of the solvent 2, δ_1 the solubility parameter of the solvent 1, and δ_2 the solubility parameter of the solvent 2.

$$\Delta H_m = V_1 \varphi_1 \varphi_2 (\delta_1 - \delta_2)^2 \qquad (1)$$

Hansen (1967) suggested the splitting of the solubility parameter into parts according to the cohesion energies due to induced dipoles (dispersion forces) δ_d (disperse part, index d), permanent dipoles (polar forces) δ_p (polar part, index p) and by hydrogen bonding forces δ_h (hydrogen part, index h). The so-called Hansen parameters or partial solubility parameters are defined as components of a vector. If these components are used as coordinates each element can be assigned to a point in space. If the norm of the vector is calculated (Eq. (2)) one obtains the “total” solubility parameter δ_t which is often equated with the Hildebrand parameter δ_{Hil}:

$$\delta_{Hil}^2 \approx \delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad (2)$$

Hansen established a scale from 1 to 6 for the state of the solvent after the adjustment for equilibrium (Hansen, 1967): 1—clear solution, 2—gel-like, thread-shaped structures, 3—solid, gelatinous, 4—very swollen, 5—little swollen, 6—insoluble. Here the solubility of 12 copolymers purchased from different manufacturers (Table 1) in 12 analytical grade solvents (Table 2) was checked. In Table 2 tabled values of Barton (1991) for the Hansen parameter, the total solubility parameter as in Eq. (2), and the Hildebrand parameter for the solvent used are given. Each sample was weighed in a 2R-vial. Two milliliters of solvent were pipetted to the 0.2 g polymer to guarantee a homogenous proportion of polymer mass to solvent. The vials were closed immediately with rubber stoppers to prevent evaporation of the solvent. Teflon coated stoppers were used to prevent the rubber from swelling. After one hour the vials were shaken and after 24 h the number according to Hansen’s solubility scale was determined by observation.

If the known solubility parameters for the substances which dissolve the polymer are shown in a diagram the area of solubility is obtained. Hansen assumed that in a diagram with the axes for δ_d, δ_p, and δ_h a spherical form would result. The “solubility sphere” is adjusted so that all solvents lie within it and all non-solvents lie outside it. The coordinates of the center of the sphere then correspond to the solubility parameters of the polymer.

Table 1
Analyzed polymers

	Polymer	Manufacturer	Batch No.
1	Poly(glycolid) (Resomer G 205)	Boehringer	95085
2	Poly(D,L-lactid(50)-co-glycolid(50))	Boehringer	26154-503H
3	Poly(D,L-lactid(50)-co-glycolid(50))	Cyanamide	8CV9107D
4	Poly(D,L-lactid(50)-co-glycolid(50))	Boehringer	260411-503
5	Poly(D,L-lactid(50)-co-glycolid(50))	Boehringer	66030
6	Poly(D,L-lactid(50)-co-glycolid(50))	Mitsui	NGLP-153
7	Poly(D,L-lactid(50)-co-glycolid(50))	Alkermes	2164-145
8	Poly(D,L-lactid(50)-co-glycolid(50))	Birmingham	P9957
9	Poly(D,L-lactid(50)-co-glycolid(50))	Purac	P14571
10	Poly(D,L-lactid(75)-co-glycolid(25))	Alkermes	92179E178
11	Poly(D,L-lactid(75)-co-glycolid(25))	Alkermes	P5317
12	Poly(D,L-lactid)	Alkermes	5054-266

Table 2
Solvents and their solubility parameters in $\sqrt{\text{MPa}}$ (Barton, 1991)

No.	Substance	$\delta_d/$	δ_p	δ_h	δ_{total}	δ_{Hil}
A	Heptane	15.3	0	0	15.3	14.9
B	Toluoene	18.0	1.4	2.0	18.2	18.2
C	Tetrahydrofuran	16.8	5.7	8.0	19.4	18.6
D	Methylacetate	15.5	7.2	7.6	18.7	19.6
E	Dichloromethane	18.2	6.3	6.1	20.3	19.8
F	Acetone	15.5	10.4	7.0	20.0	20.2
G	1,4-Dioxane	19.0	1.8	7.4	20.5	20.3
H	Pyridine	19.0	8.8	5.9	21.8	21.9
I	Formic acid	14.3	11.9	16.6	24.9	24.7
J	Propylene carbonate	20.1	18.0	4.1	27.3	27.2
K	Methanol	15.1	12.3	22.3	29.6	29.7
L	Glycerol	17.4	11.0	26.0	32.9	33.7

Table 3
Left: solvents and nonsolvents used as mixtures; right: copolymers of different ratios of lactide:glyoclide

ID	Non-solvent	Solvent	ID	Polymer	Manufacturer	M_w
A	Methanol	Propylene carb.	I	PLA	Boehringer	35000
B	Toluene	Propylene carb.	II	85:15	Alkermes	75000
C	Toluene	Dioxane	III	75:25	Alkermes	75000
D	Methanol	Dioxane	IV	50:50	Alkermes	50000

The adjustment of the sphere follows in two-dimensional projections. For this adjustment two criteria must be fulfilled. First, a minimum number of solvents must lie outside the sphere, and at the same time a minimum number of non-solvents must lie within the sphere. For this purpose the surface of the sphere is shown in each case as a projection in one direction of space. In these views the centers and radii of the solubility spheres can be ascertained by moving the circles and by changing their size. To improve the sphere-fitting, some of the solvents were used as mixtures. According to a simple mixing rule solvents with specific solubility parameters δ_{mix} can be created from volume fractions φ of two solvents. Eq. (3) can also be applied to partial solubility parameters (Barton, 1991).

$$\delta_{mix} = \varphi_1\delta_1 + \varphi_2\delta_2 \qquad (3)$$

Table 3 (left) lists the chosen non-solvents and solvents. For each combination volume ratios of (a) 3:1, (b) 2:2, and (c) 1:3 were mixed. Solubility of different copolymers was rated to clear solution, interaction (partially or completely gelatinous), insoluble.

2.2. Turbidimetric titration experiments

If one adds to a polymer solution a fixed amount of a liquid which does not dissolve the polymer, the polymer precipitates. The mass proportion of the components used provide information on the interaction between polymers and can be used to characterize PLG and microspheres (Hausberger and DeLuca, 1995). Suh and Clarke (1967) developed a method using these data by which it is possible to calculate the solubility parameter as an absolute value. The basis for this is the relation between the Flory–Huggins parameter and the solubility parameter. The Flory–Huggins parameter can be split into enthalpic and entropic parts, whereby the enthalpic part χ_h describes the interaction between the molecules of the polymer and the solvent. The enthalpic part is linked to solubility parameter (Shinoda, 1978) as follows in Eq. (4). Here υ denotes the molar volume of the solvent, R the general gas constant and T the temperature in Kelvin.

$$\chi_h = \frac{\upsilon_{sol}(\delta_{sol} - \delta_{polymer})^2}{RT} \qquad (4)$$

For turbidimetric titration two non-solvents for the polymer are chosen so that one (index 1) has a solubility parameter lower than the solubility parameter of the solvent (index 2) and the other (index 3) has a higher solubility parameter. Both non-solvents should dissolve each other completely. Each non-solvent is mixed with the solvent. The molar volume v of these mixtures (index m) is approximated by Eq. (5).

$$v_{\mathrm{m,low}} = \frac{v_1 v_2}{\varphi_1 v_2 + \varphi_2 v_1}; \quad v_{\mathrm{m,high}} = \frac{v_2 v_3}{\varphi_2 v_3 + \varphi_3 v_2} \qquad (5)$$

One of the non-solvents is added to the polymer solution until turbidity. At the point of turbidity the polymer possesses the so-called apparent solubility parameter $\delta_{\mathrm{app,p}}$. The apparent solubility parameter and the Flory–Huggins parameter can be set equal in both (turbid) mixtures. After rearranging the equations for the Flory–Huggins parameter one can substitute χ_{h}. Finally the apparent solubility parameter is calculated by Eq. (6), as the solubility parameter of the mixtures is calculated according to Eq. (3).

$$\delta_{\mathrm{app,p}} = \frac{\delta_{\mathrm{m,low}}\sqrt{v_{\mathrm{m,low}}} + \delta_{\mathrm{m,high}}\sqrt{v_{\mathrm{m,high}}}}{\sqrt{v_{\mathrm{m,low}}} + \sqrt{v_{\mathrm{m,high}}}} \qquad (6)$$

Five different solvents of analytical grade were tested: methylacetate, tetrahydrofuran, acetone, dichloromethane and 1,4-dioxane. The polymer was dissolved (0.3 g in 10 ml) in a closed beaker using a magnetic stirrer for one hour. Four combinations of non-solvents were used: hexane/methanol, heptane/methanol, hexane/butanol, and heptane/butanol. The titration of the non-solvent was stopped at the first observed signs of turbidity. In order to determine the solubility parameter of a polymer, the apparent solubility parameters are each entered over the solubility parameters of the solvents which are used, and a correlating straight line is calculated. Additionally, the line for $\delta_{\mathrm{app}} = \delta_{\mathrm{sol}}$ is plotted and at the intersection of both straight lines the solubility parameter is read.

Three different batches of PLGA (50:50, $M_{\mathrm{w}} \approx 65000$, Alkermes) were analyzed. Here the described method was extended to determine also the partial solubility parameter using the described calculation the for partial solubility parameter. The partial solubility parameters for PLA and PLGA with lactide:glycolide ratios of 85:15, 75:25, and 50:50 were determined.

2.3. Group contribution method

The partial solubility parameters can be calculated from the contributions of the functional groups for cohesion energy F and molecular volume v, which can be found, for instance, in tables drawn up by Barton (1991). In Eq. (7), the numerator is in each case the sum of the group contributions of the cohesion energies and in the denominator the sum of the group contributions of the molar volumes v of the functional groups (Barton, 1991).

$$\delta_{\mathrm{d}} = \frac{\sum_i^i F_{\mathrm{d}}}{\sum_i^i v}; \quad \delta_{\mathrm{p}} = \frac{\sqrt{\sum_i^i F_{\mathrm{p}}^2}}{\sum_i^i v}; \quad \delta_{\mathrm{h}} = \sqrt{\frac{\sum_i -{}^i U_h}{\sum_i^i v}} \qquad (7)$$

3. Results

3.1. Results of swelling experiments

Polyglycolide did not dissolve in any solvent (Table 4, column 1). None of the polymers was soluble in heptane or glycerol. Most of the polymers only swelled in toluene and methanol (rows B and K). The differences for lactide:glycolide ratios of 50:50 (columns 2–9) or 75:25, and pure PLA were not significant.

Fig. 1 shows ideal specimens for each solubility state. Often it is difficult to rate between adjacent numbers of the scale. Therefore the scale was simplified to 3 states (1—soluble, 2—interaction, 3—insoluble) for further experiments of mixed solvents (Table 5).

Center coordinates and radii are listed in Table 6. It was observed that:

- the disperse fraction of solubility parameter was independent from copolymer ratio,
- the increase of the glycolide fraction slightly increased the solubility for polar substances,

Fig. 1. States of decreasing solubility corresponding to the solubility numbers from 2 to 6 (left to right).

Table 4
Results of swelling experiments for all combination of polymer and solvent

	1	2	3	4	5	6	7	8	9	10	11	12
A	6	6	6	6	6	6	6	6	6	6	6	6
B	6	5	5	5	5	5	1	5	5	4	4	5
C	6	4	2	2	3	1	3	2	1	1	1	3
D	6	1	1	1	1	1	1	1	1	1	1	2
E	6	1	1	1	1	1	1	1	1	1	1	1
F	6	1	1	2	1	2	1	1	1	1	1	2
G	6	1	1	1	1	1	2	1	1	1	1	1
H	6	1	2	1	2	2	1	1	1	2	1	3
I	6	1	2	1	2	2	1	1	1	2	1	3
J	6	1	1	1	1	1	2	2	1	1	2	1
K	6	5	5	5	5	5	5	5	5	5	5	5
L	6	6	6	6	6	6	6	6	6	6	6	6

Table 5
Solubility states for different solvent–non-solvent mixtures

A	I	II	III	IV	B	I	II	III	IV
a	1	1	2	2	a	1	1	1	2
b	1	1	1	2	b	1	1	1	1
c	1	1	1	1	c	1	1	1	1
C	I	II	III	IV	D	I	II	III	IV
a	1	1	1	2	a	1	1	1	2
b	1	1	1	2	b	1	1	1	1
c	1	1	1	1	c	1	1	1	1

Table 6
Solubility parameters of some copolymers with different ratio of lactide:glycolide (L:G)

L:G	100:0	85:15	75:25	50:50
δ_d	17.4	17.4	17.4	17.4
δ_p	7.6	8.3	8.3	9.1
δ_h	10.5	9.9	9.9	10.5
δ_{total}	21.7	21.7	21.7	22.3
R	8.4	8.0	7.8	7.5

- the hydrogen fraction of solubility parameter was slightly higher for PLGA at a comonomer ratio of 50:50 than for 85:15 and 75:25,
- the radius of the solubility sphere decreased with an increase of glycolide fraction.

3.2. *Results of turbidimetric titrations*

Fig. 2 shows one example of the determination of the solubility parameter. As observed by Jayasri and Yaseen (1982) only combinations with butanol led to an intersection of the lines.

Figs. 3 and 4 compare three polymer batches. From Fig. 3 a slightly lower apparent solubility parameter for batch P11414 in acetone was observed. But in Fig. 4 the difference can be seen for dichloromethane. Compared to the quality of the fit these differences are not significant.

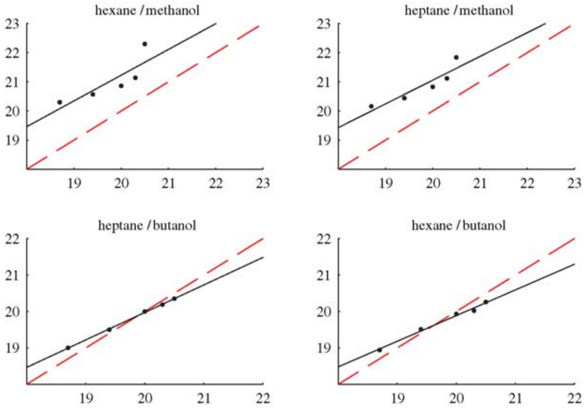

Fig. 2. Example of graphical determination of solubility parameter (x-axis δ_{sol}, y-axis δ_{app}, both in $\sqrt{\text{MPa}}$).

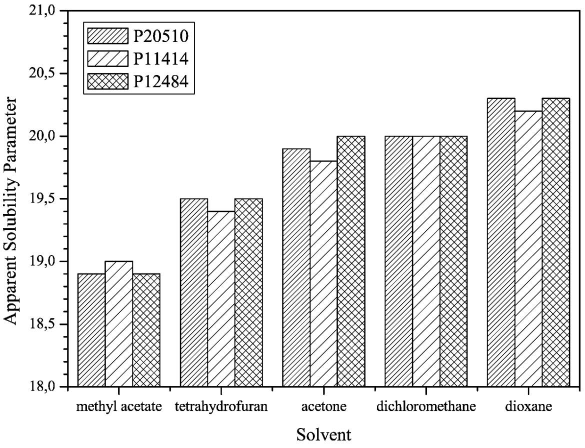

Fig. 3. δ_{app} in $\sqrt{\mathrm{MPa}}$ for the combination hexane/butanol for three batches PLGA.

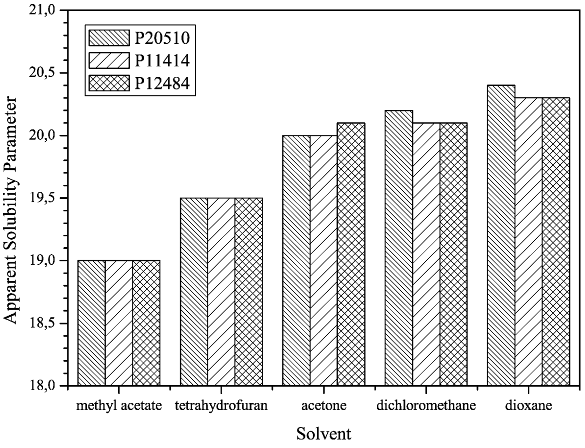

Fig. 4. δ_{app} in $\sqrt{\mathrm{MPa}}$ for the combination heptane/butanol for three batches PLGA.

Table 7 lists the partial solubility parameters for different copolymer ratios of lactide:glycolide. The dimensions of each partial parameter are comparable to those determined by the other methods. The values of δ_{p} are very low and seem unrealistic. Due to the method of calculation, the value of the total solubility parameter is lower than that of the solubility parameter obtained above.

Table 7
Partial solubility parameters for different ratios of lactide:glycolide determined by turbidity titration

	100:0	85:15	75:15	50:50
δ_{d} ($\sqrt{\mathrm{MPa}}$)	15.7	15.8	15.8	16.4
δ_{p} ($\sqrt{\mathrm{MPa}}$)	3.5	3.7	3.5	3.6
δ_{h} ($\sqrt{\mathrm{MPa}}$)	11.1	9.5	9.1	8.7
δ_{total} ($\sqrt{\mathrm{MPa}}$)	19.8	19.8	19.8	19.9

Table 8
Partial solubility parameters for different ratios of lactide:glycolide calculated by group contribution method L:G

	100:0	85:15	75:15	50:50	0:100
υ_{m} (cm^3/mol)	56.4	53.8	52.0	47.7	38.9
δ_{d} ($\sqrt{\mathrm{MPa}}$)	15.8	16.0	16.1	16.4	17.0
δ_{p} ($\sqrt{\mathrm{MPa}}$)	8.7	9.3	9.7	10.7	12.6
δ_{h} ($\sqrt{\mathrm{MPa}}$)	11.1	11.4	11.7	12.3	13.4
δ_{total} ($\sqrt{\mathrm{MPa}}$)	21.1	21.7	22.1	23.1	25.0

3.3. *Results of group contribution method*

The calculation method was described by Barton (1991) for polymers but not for copolymers. A “mixing rule” for the calculation of the solubility parameters for copolymers is not given by Barton. Therefore, the partial solubility parameters were calculated for PLA and polyglycolide and the fractions according to the ratio of lactide:glycolide weighed. Results are summarized in Table 8.

4. Discussion

In this paper three methods were identified and employed for determining the partial solubility parameters of PLGA. These methods were:

- Swelling experiments
- Turbidity titration
- The group contribution method

Using swelling experiments the partial solubility parameters were determined for copolymers of different lactide and glycolide ratios. The observation that higher fractions of lactide lead to higher solubility in general was confirmed by the determined radii of solubility spheres. Nevertheless, no quantitative conclusions could be drawn regarding the amount of non-solvent required for demixing during microencapsulation. In spite of improved fitting of the solubility sphere by mixtures of solvents and non-solvents the exactness of the method is questionable as subjective decisions on the

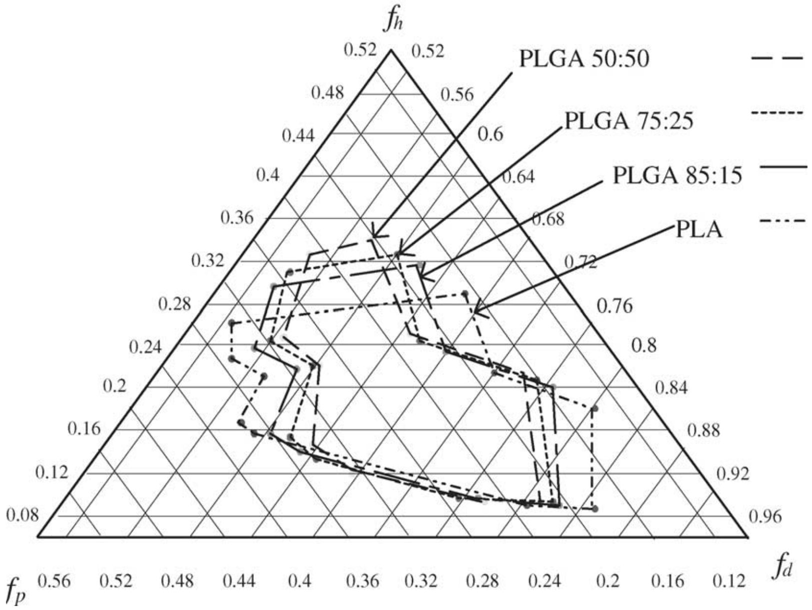

Fig. 5. Zoomed solubility map of PLA and PLGA with different comonomer ratios.

assignment of coordinates of solvents and non-solvents influence the position of the solubility sphere.

The turbidimetric titrations allowed determination of solubility parameters for three batches of poly(lactide(50)-co-glycolide(50)). Although one of these batches produced no microparticles, the measured differences of solubility parameter were not significant. The method of parameter calculation was also applied on partial solubility parameters. The determined polar fraction of the solubility parameter showed an unrealistically low value.

The group contribution methods enabled the arithmetical estimation of the partial solubility parameters. The calculation carried out for PLGA used a “mixing rule” to account for the proportions of PLA and PGA. The total solubility parameter determined for all copolymers by group contribution compared to those of the swelling method are very similar but values for turbidimetric titrations were always lower by about $2.0\,\sqrt{\mathrm{MPa}}$.

For the presentation of partial solubility the fractional solubility parameters are used (Teas, 1969). These are evaluated from partial solubility parameters and plotted into a triangle diagram—a so-called solubility map. It can be clearly seen from Fig. 5 that the solubility area becomes smaller with increasing glycolide amount. As a result the choice of alternative solvents gets smaller with increasing glycolide amount.

5. Conclusion

In summary, it was shown that solubility parameters and partial solubility parameters for copolymers made from lactide and glycolide can be determined. Results were compiled in solubility maps which are handy when choosing solvents for a polymer.

Turbidity titration appeared to be the most precise method but measured values have to be rounded to the same accuracy of the tabulated solubility parameters that have to be used in the calculation. The accuracy obtained is only suitable for qualitative assessments. The low degree of accuracy does not allow these methods to be used for differentiating between batches of the same polymer type. The fact that the cohesion end energy densities of polymers cannot be directly measured is the main reason for this limitation. Direct measuring is not possible as the cohesion strength is greater than the atomic linking strength, and the polymer molecules would decompose before evaporation (Barton, 1991; Siemann, 1992). Therefore other measurable factors, such as for example the chemical potential, appear to be more suitable for the quantitative description of the interactions between polymer and solvent.

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