

## Effect of Mixed Solvents on Polymer Conformation – Correlation between the Hildebrand/Hansen Solubility Parameters and the Intrinsic Viscosity of Polymer Solutions

Claus Greve Madsen<sup>1</sup>, Anders Skov<sup>1</sup>, Lene Jørgensen<sup>1</sup>, Stefania Baldursdottir<sup>1</sup>, Natalie J. Medicott<sup>2</sup>

<sup>1</sup>Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

<sup>2</sup>School of Pharmacy, University of Otago, Dunedin, New Zealand.

### ABSTRACT

This study investigated the effect of solvents on the uncoiling of four different linear polymers. Solubility parameters were used to represent solubility power towards the polymers, while the intrinsic viscosity of the polymer solution was used as a representation of polymer conformation/uncoiling. This approach may be used to control polymer uncoiling.

### INTRODUCTION

When a polymer uncoils in a solvent, its chains interact with the surroundings, thereby increasing the viscosity of the solution. As the hydrodynamic volume of the polymer increases with greater uncoiling, the intrinsic viscosity,  $[\eta]$ , of the polymer also increases. Thus, a polymer will have a greater intrinsic viscosity in a solvent in which it is readily soluble, than it would have in solvent in which it is only slightly soluble.

Solubility parameters allow for numeric representation of the solubility of solvents/solutes, by assigning a value to solvent/solute based on their respective cohesive energies<sup>1, 2</sup>. Following the principle of solubility parameters, the solute should readily dissolve if the solvent and the solute have similar solubility parameter value, (making the solvent a ‘good solvent’). Con-

versely; the solute should be insoluble in the solvent if the solubility parameters are too different, (making the solvent a ‘bad solvent’). The solubility parameters may thereby be used to predict whether or not a solute will dissolve in a given solvent. While the original Hildebrand solubility parameters were calculated solely by the heat of evaporation<sup>3, 4</sup>, the newer Hansen solubility parameters divided the total cohesion energy of a liquid, into three individual aspects: The dispersion cohesive energy,  $E_D$ , the polar cohesive energy,  $E_P$  and the electron exchange parameter,  $E_H$ , with the total cohesion energy,  $E$ , being the sum of the three<sup>5</sup>.

In this study, the intrinsic viscosity of a series of polymers was measured (using an Ubbelohde viscometer), and plotted against the solubility parameter of the solvent. Thereby, evaluation of polymer the uncoiling in different solvents was possible, ultimately allowing for modification of polymer uncoiling in solvent mixtures.

### MATERIALS AND METHODS

#### Polymers and solvents

Polycaprolactone (PCL) [CAS#: 24980-41-4]; 704105-100g [lot#: MKBH4957V], Sigma-Aldrich; ethylene-vinyl acetate copolymer (EVA) (Elvax® 40W [CAS#: 24937-78-8]; Du Pont); Poly(DL-lactide-

co-glycolide) (PLGA) [CAS#: 26780-50-7], [50:50 Carboxylated End Group (nominal), Lactel, Part # B6013-2P] and PLGA-7520 (75:25 %) [CAS#: 34346-01-5], 820-11976 [Lot#: KLF0935], Wako Pure Chemical Industries, Ltd were dissolved in either the pure solvent, or mixtures, of: Dichloromethane (DCM) [Ph.Eur. analytical reagent, Merck]; acetone (ACE) [ $\geq 99.8$  %, Ph.Eur. analytical reagent, Merck]; ethanol (EtOH) [96 %, Kemetyl A/S] or demineralised water (H<sub>2</sub>O).

### Intrinsic viscosity measurement

Viscosity measurements of the polymer solutions was performed in dilute solution, by using an Ubbelohde Semi-Micro dilution viscometer (No. 50, N212, Cannon instrument Company, USA) at  $25 \pm 0.2$  °C. The flow time ( $t$ ) of the solution and pure solvent ( $t_0$ ), was measured in 8 different concentrations, and each measurement repeated three times. From these, the relative viscosity ( $\eta_{rel}$ ) was calculated (Eq. 1), and the specific viscosity ( $\eta_{sp}$ ) obtained (Eq. 2).

$$\eta_{rel} = \frac{t}{t_0} \quad (1)$$

$$\eta_{sp} = \eta_{rel} - 1 \quad (2)$$

Finally, the intrinsic viscosity was calculated, by extrapolation of the specific viscosity divided by the polymer concentration ( $\frac{\eta_{sp}}{C}$ ,  $C$  being the polymer concentration in g/ml) as a function of  $C$  (Huggins plot), to a concentration of zero ( $C_0$ ).

### Solubility parameters

The solubility parameters of the pure solvents were gathered from existing literature<sup>6</sup>. The solubility parameters of the blended solvents were calculated by averaging the solubility parameter values of the individual solvents ( $\delta_i$ ) by their volume fraction ( $\phi_i$ ) (Eq. 3), following the approach suggested for the Hildebrand solubility parameters by Barton<sup>2</sup> in 1975.

$$\bar{\delta} = \sum_i \phi_i \delta_i \quad (3)$$

As the solubility parameters are determined by the heat of evaporation, direct measurement of the polymers were not possible. Therefore, the solubility parameters of the polymers were calculated from their intrinsic viscosities in different solvents. This approach builds on a correlation between the intrinsic viscosity and the Hansen solubility parameters, determined in 1985 by Van Dyk et al.<sup>7</sup>; with the method of calculation later being described by Segarceanu and Leca<sup>8</sup> in 1997 (Eq. 4-6). The method allows for calculating the three different aspects of the Hansen solubility parameter (dispersive,  $\delta_D$ ; polar,  $\delta_P$  and electron exchange  $\delta_H$ ) of a polymer (subscript 'P'), from the solubility parameters of the solvent (subscript 'i'), and the intrinsic viscosity of the polymer in the solvent ( $[\eta]_i$ ).

$$\delta_{DP} = \frac{\sum(\delta_{Di}[\eta]_i)}{\sum[\eta]_i} \quad (4)$$

$$\delta_{PP} = \frac{\sum(\delta_{Pi}[\eta]_i)}{\sum[\eta]_i} \quad (5)$$

$$\delta_{HP} = \frac{\sum(\delta_{Hi}[\eta]_i)}{\sum[\eta]_i} \quad (6)$$

With the total solubility parameter ( $\delta_T$ ) being the square root of the squared and summed solubility parameter aspects, as proposed by Hansen<sup>5</sup> (Eq. 7).

$$\delta_T^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (7)$$

Solvents unable to dissolve the polymer were assumed to have a zero weighing factor.

## RESULTS AND DISCUSSION

The Hildebrand and Hansen solubility parameters for the solvents, solvents mixtures and polymers were obtained from literature<sup>6</sup> or calculated (Table 1), and plotted against the intrinsic viscosities of the polymers.

Table 1. Hildebrand and Hansen solubility parameters of solvents (obtained from Barton<sup>6</sup>), mixed solvents (calculated from the pure solvents) and polymers (calculated from their intrinsic viscosity<sup>8</sup>).

Solvent	Hildebrand solubility parameter [MPa <sup>1/2</sup> ]	Hansen solubility parameter [MPa <sup>1/2</sup> ]			
	$\delta$	$\delta_T$	$\delta_D$	$\delta_P$	$\delta_H$
Acetone (ACE)	19.70	20.00	15.50	10.40	7.00
Dichloromethane (DCM)	20.20	20.30	18.20	6.30	6.10
Ethanol (EtOH)	26.20	26.50	15.80	8.80	19.40
Demineralised water (H <sub>2</sub> O)	48.00	47.80	15.60	16.00	42.30
50/50 % DCM/ACE	19.95	20.18	16.85	8.35	6.55
95/5 % DCM/EtOH	20.50	20.61	18.08	6.43	6.77
90/10 % DCM/EtOH	20.80	20.92	17.96	6.55	7.43
85/15 % DCM/EtOH	21.10	21.23	17.84	7.31	8.10
98.25/1.75 % ACE/H <sub>2</sub> O	20.20	20.49	15.50	10.50	7.62
97/3 % ACE/H <sub>2</sub> O	20.55	20.83	15.50	10.57	8.06
95/5 % ACE/H <sub>2</sub> O	21.12	21.39	15.51	10.68	8.77
90/10 % ACE/H <sub>2</sub> O	22.53	22.78	15.51	10.96	10.53
Polymer	$\delta$	$\delta_T$	$\delta_D$	$\delta_P$	$\delta_H$
PCL	20.57	20.70	-	-	-
EVA	20.70	20.57	-	-	-
PLGA 50:50	20.20	20.43	-	-	-
PLGA 75:25	20.44	20.64	-	-	-

PCL solutions of DCM had the highest intrinsic viscosity of the pure solvents, while the polymer was insoluble in both ACE (Figure 1) and EtOH (not shown). PCL in mixtures of 50/50 % DCM/ACE yielded an intrinsic viscosity intermediate of pure DCM and ACE, corresponding well with its solubility parameters being intermediate of

those of the pure solvents (Figure 1). PCL solutions in DCM with moderate amounts of EtOH (5-15 %) yielded higher intrinsic viscosities than DCM alone, even though PCL was insoluble in pure EtOH (Figure 1). However, a 98.25/1.75 % ACE/H<sub>2</sub>O mixture failed to dissolve the polymer, even though this mixture had solubility parameters comparable to that of DCM (Figure 1, Table 1). It is thereby inferred that the polymer must be soluble in one of the components of a solvent mixture for the parameters to be applicable, regardless of the resulting solubility parameters of the mixture.

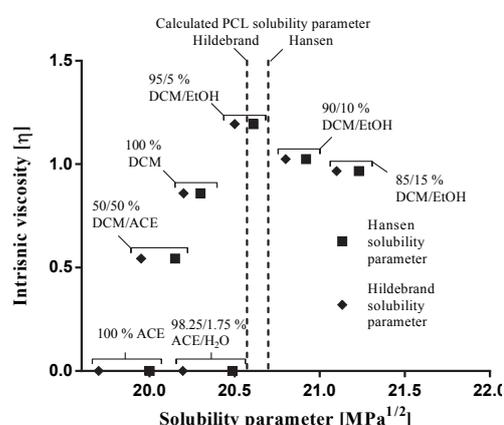


Figure 1. The intrinsic viscosity of PCL in different pure and mixed solvents (ACE: Acetone, DCM: Dichloromethane, EtOH: Ethanol), plotted against the solubility parameters of the solvents/mixtures. The calculated solubility parameter of the polymer is indicated by a broken vertical line.

Solutions of EVA in DCM yielded the highest intrinsic viscosity of the pure solvents (Figure 2), while the polymer was insoluble or only slightly soluble in EtOH and ACE (not shown). EVA in mixtures of 50/50 % DCM/ACE yielded higher intrinsic viscosities than that of pure ACE, and lower than pure DCM. This corresponds well with the mixture having a total solubility parameter closer to that of EVA, than pure ACE, but not as close as that of pure DCM (Table 1). EVA solutions of DCM mixed with

moderate amounts of EtOH (5-15 %) had the highest intrinsic viscosities, with the 90/10 % DCM/EtOH mixture having the highest intrinsic viscosity of all (Figure 2), despite the 95/5 % DCM/EtOH mixture having a total solubility parameter closer to that of EVA (Table 1). The difference in intrinsic viscosity is however only slight, and may be within the margin of error, or may be explained by the mixture's difference in  $\delta_H$ , which is the solubility parameter aspect that varies the most between the mixtures (Table 1).

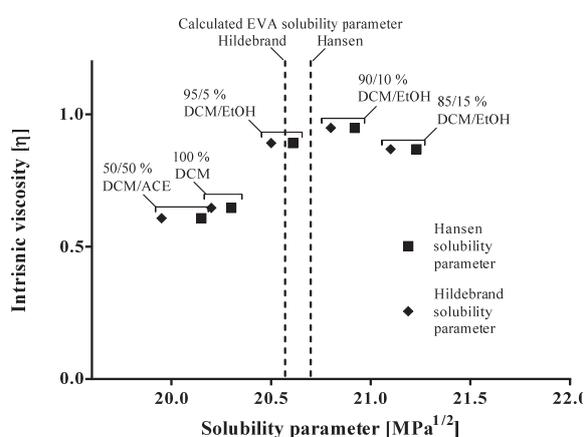


Figure 2. The intrinsic viscosity of EVA in different pure and mixed solvents (ACE: Acetone, DCM: Dichloromethane, EtOH: Ethanol) plotted against the solubility parameters of the solvents/mixtures. The calculated solubility parameter of the polymer is indicated by a broken vertical line.

For solutions of PLGA (50:50 DL:GA) DCM yielded the highest intrinsic viscosity, of the pure solvents, and ACE the lowest (Figure 3), with the polymer being insoluble in H<sub>2</sub>O (not shown). A 50/50 % DCM/ACE solvent mixture yielded an intrinsic viscosity in between the pure DCM and ACE (Figure 3). By mixing ACE with small amounts of H<sub>2</sub>O (1.75-3 %) it was possible to produce solutions with intrinsic viscosities greater than those of both pure ACE and the 50/50 DCM/ACE mixture (Figure 3). However, adding greater amounts of H<sub>2</sub>O to

ACE (5-10 %) resulted in solutions with intrinsic viscosities lower than that of pure ACE (Figure 3), corresponding to the solubility parameter difference between the polymer and mixture becoming greater with increasing amounts of H<sub>2</sub>O. The pure DCM and the mixture of ACE with 1.75 % H<sub>2</sub>O had the same Hildebrand solubility parameter (Table 1), but yielded different intrinsic viscosities. The mixture's Hansen solubility parameter was closer to the Hansen solubility parameter of the polymer (Table 1), yet failed to show higher intrinsic viscosities. The reason for this discrepancy may be found in differences of the solvents individual Hansen solubility aspects; the addition of H<sub>2</sub>O to ACE primarily increases  $\delta_H$ , as H<sub>2</sub>O is much higher in this aspect than ACE (Table 1). The differences in the solubility parameters of ACE mixed with 3 % H<sub>2</sub>O, and those of the polymer, were approximately the same as the differences between the solubility parameters of the polymer and the 50/50 DCM/ACE mixture (Figure 3). And thus the mixtures yield similar intrinsic viscosity.

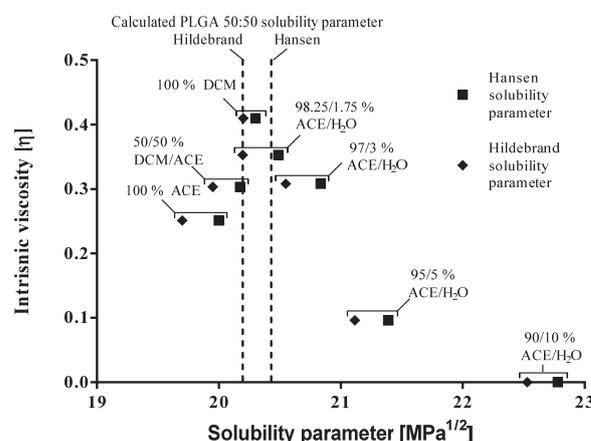


Figure 3. The intrinsic viscosity of PLGA 50:50 in different pure and mixed solvents (ACE: Acetone, DCM: Dichloromethane) plotted against the solubility parameters of the solvents/mixtures. The calculated solubility parameter of the polymer is indicated by a broken vertical line.

Similar to the PLGA 50:50 (Figure 3), solutions of PLGA (75:25 DL:GA), showed highest intrinsic viscosity for DCM, and lowest for ACE of the pure solvents (Figure 4). Also similar to the PLGA 50:50, solutions of ACE mixed with moderate amounts of H<sub>2</sub>O (5-10%), yielded the lowest intrinsic viscosities (Figure 4), corresponding well with the difference between the total solubility parameters of the mixture and polymer becoming greater with increasing amounts of H<sub>2</sub>O (Table 1). This is to be expected, as the chemistry of the PLGA polymers is very similar. However, PLGA 75:25 solutions of 50/50 % DCM/ACE mixtures yielded a lower intrinsic viscosity than that of pure ACE (Figure 4), despite the mixture having total solubility parameters closer to that of the polymer (Table 1), and therefore should have a higher intrinsic viscosity than the mixtures constituents, as for PLGA 50:50 (Figure 3). This cannot be explained by a difference in solubility parameter aspects, as all aspects of the mixture are closer to those of pure DCM than those of pure ACE (Table 1). The difference is however slight, and may therefore be within the margin of error.

Further comparison of the PLGA polymers would elucidate differences in their solubility parameters. Therefore, mixtures of ACE with lower amounts of H<sub>2</sub>O should have been tested, as for PLGA 50:50 (Figure 3).

## CONCLUSION

Measured intrinsic viscosities were found to be in good agreement with the likeness of the solvent's solubility parameters to those of the polymer. Employing solubility parameters to predict the uncoiling of a polymer in solution was found to be plausible. However when doing so, all aspects of the solubility parameters should be considered. Therefore, use of the Hansen solubility parameters may be superior to the Hildebrand solubility parameters.

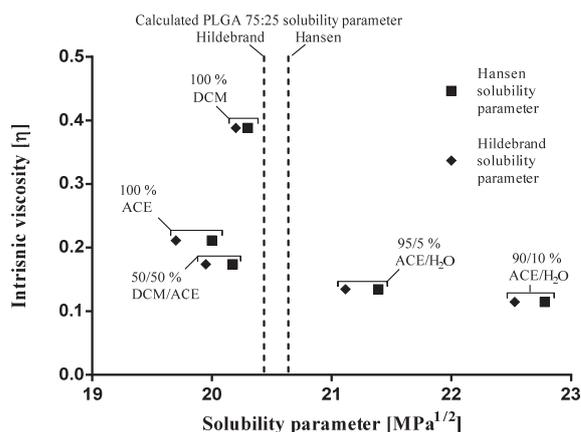


Figure 4. The intrinsic viscosity of PLGA 75:25 in different pure and mixed solvents (ACE: Acetone, DCM: Dichloromethane) plotted against the solubility parameters of the solvents/mixtures. The calculated solubility parameter of the polymer is indicated by a broken vertical line.

## REFERENCES

- Burke, J., *Solubility Parameters: Theory and Application*. 1984, The American Institute for conservation: The Book and Paper Group.
- Barton, A.F.M., *Solubility parameters*. Chemical Reviews, 1975. **75**(6): p. 731-753.
- Belmares, M., et al., *Hildebrand and Hansen solubility parameters from molecular dynamics with applications to electronic nose polymer sensors*. J Comput Chem, 2004. **25**(15): p. 1814-26.
- Hansen, C.M., *50 Years with solubility parameters—past and future*. Progress in Organic Coatings, 2004. **51**(1): p. 77-84.
- Hansen, C.M., *Solubility Parameters - An Introduction*, in *Hansen Solubility Parameters*. 1999, CRC Press.
- Barton, A.F.M., *Practical Liquid Solubility Scales*, in *Handbook of Solubility Parameters and Other Cohesion*

*Parameters*, 1, Editor. 1984, CRC Press, Inc.: Florida. p. 139-200.

7. Van Dyk, J.W., H.L. Frisch, and D.T. Wu, *Solubility, solvency, and solubility parameters*. Industrial & Engineering Chemistry Product Research and Development, 1985. **24**(3): p. 473-478.

8. Segarceanu, O. and M. Leca, *Improved method to calculate Hansen solubility parameters of a polymer*. Progress in Organic Coatings, 1997. **31**(4): p. 307-310.