

VISCOSITY MEASUREMENTS OF VARIOUS POLYMER/SOLVENT SOLUTIONS AND THEIR RELATION WITH ADIMENSIONAL NUMBERS INVOLVED IN THE ANTISOLVENT SAS TECHNIQUES

Arlette Vega-González*¹, Pascale Subra-Paternault ¹
Francesco Nudda^{1,2}, Bruno Marongiu ²

¹ Laboratoire d'Ingénierie des Matériaux et des Hautes Pressions, C.N.R.S., Institut Galilée, Université Paris 13, 99 Avenue Jean Baptiste Clément, 93430 Villetaneuse, France

² Dipartimento di Scienze Chimiche, Università di Cagliari, Cittadella Universitaria di Monserratto, 09042 Cagliari, Italy

vega@limhp.univ-paris13.fr - fax : 33 1 49 40 34 14

Carbon dioxide has been used as an antisolvent for the production of polymeric particles. However, development of experimental conditions to control particle size and morphology of this kind of products is lacking.

To help understanding the influence of spraying conditions on particle formation, kinematic viscosity of liquid solutions of two polymers were measured. Viscosity measurements were carried out at different temperatures (25°C , 30°C and 35°C). The polymers studied were L-PLA and DL- PLGA. For L-PLA, solutions were prepared in pure dichloromethane since this solvent is largely used in spraying processes. In case of DL-PLGA, the polymer was dissolved in three different solvents, e.g. ethyl acetate, acetone and dichloromethane. The viscosity data were further used to compare the effect of polymer, organic solvent and solution concentration on particle morphology, through calculations of the dimensionless numbers of Reynolds and Weber.

INTRODUCTION

Polymer microparticles and fibres are of interest as potential drug delivery systems and biodegradable filler material. Different organic and inorganic materials have been processed employing the supercritical fluids as solvents or antisolvents. Materials having different morphologies - particles, fibres, films - have been obtained with different techniques. When compressed gases are used as antisolvents, and a dissolved solute is sprayed into a compressed gas, the process is known as supercritical antisolvent process (SAS). This process generally uses CO₂ as the antisolvent, and the operating pressure and temperature are usually selected so the solvent and the antisolvent are completely miscible.

Few studies concerning the mechanisms controlling polymer particle morphology when using supercritical fluids as antisolvents have been published. The first parametric studies were carried out by Dixon et al.[1] and Randolph et al.[2], and they indicate that a transition from microparticles to microfibrils occurs with an increase in solution viscosity, or atomization time, for a given solution velocity, pressure and temperature. This dependence on

viscosity results from the transition to nondilute polymeric solutions, where the polymer has a large effect on the fluids properties, such as surface tension and non-Newtonian behavior, as the solvent concentration decreases [3]. The critical concentration causing this transition will vary with the polymer [4]. More recently, Lengsfeld et al.[3] studied the mechanisms governing particle morphology in polymers and found that presumably, microparticle formation results from gas phase nucleation and growth within the expanding plume, rather than nucleation within discrete liquid droplets. Lately, Pérez de Diego et al.[5] provided experimental evidence for the hypothesis that when processing polymer solutions there are two different mechanisms of droplet formation governing the final size of the precipitated particles: hydraulic atomization and liquid-liquid phase split. They demonstrate that when working at conditions below the mixture critical pressure (MCP) it was possible to produce polymer particles. At conditions where the two fluids are completely miscible, smaller particles and microfibers were obtained.

In this work, viscosity measurements of two different polymers, poly lactic acid and poly-lactide co-glycolide were carried out in order to compare the possible influence of different parameters such as polymer type or concentration, on the atomization process, and thus on particle morphology. Calculations of the dimensionless numbers of Reynolds and Weber have been used in order to compare the different experimental conditions.

I- MATERIALS AND METHODS

I.1 Materials

L-Poly(lactic acid) (L-PLA, MW : 100 000) was obtained from Galastic Laboratories, Belgium. Poly(DL-lactide-co-glycolide) (PLGA, 50:50, inherent viscosity 0.55-0.75) was obtained from Aldrich, France. Methylene chloride (DCM, Chromanorm grade), acetone (ACE, Normapur grade) and ethyl acetate (ETHY, Chromanorm grade) were obtained from Prolabo (France) and used without additional purification. CO₂ (99%, industrial grade) was purchased from Air Liquide (France).

I.2 Methods

Viscosity measurements

Viscosity measurements were carried out using a Ubbelohde-type capillary viscometer, they were performed at 25, 30 and 35°C. All the polymer solutions were used immediately after preparation. The viscometer was immersed in a constant temperature bath that was controlled to within $\pm 0.1^\circ\text{C}$, the efflux times were reproducible to $\pm 0.2\%$, and the flow times were measured with an accuracy of $\pm 0.06\text{ s}$. For the molecular weight investigated, shear effects were assumed to be negligible. The concentration dependence of the viscosity of polymer solutions was followed by the well-known Huggins equation [6] :

$$\eta_{sp} / c = [\eta] + k_H [\eta]^2 c \quad (1)$$

where η_{sp} is the specific viscosity, c is the solution concentration, $[\eta]$ is the intrinsic viscosity and k_H is a constant.

The intrinsic viscosities - which reflect the capability of a polymer in solution to enhance the viscosity of the solution - were obtained from plots of the η_{sp} / c ratio against the polymer concentration, with subsequent extrapolation to infinite dilution.

Precipitation experiments

The apparatus used for the experiments was operated in a semi-continuous mode. The description of the experimental set-up can be found elsewhere [7].

II- RESULTS AND DISCUSSION

II.1 Viscosity measurements

The viscosity measurements carried out allowed to represent plots of the η_{sp}/c ratio against the polymer concentration. These plots (which are not presented here) show that a linear relationship exists. Then, from equation (1) it is possible to calculate the viscosity parameters of the different systems. These parameters are presented in Table 1. In this table, C^* corresponds to the overlap concentration, at which polymer coils begin to overlap each other (separating semi-dilute and dilute regimes in polymer solutions). C^* can be approached from the reciprocal of the intrinsic viscosity ($C^* = 1/[\eta]$) [8].

The constant k_H is a measure of the solvent quality. When the polymer is in a good solvent, its value is near 1/3, and it can increase up to 0.5 – 1 for solutions in poor solvents [9]. Results presented in Table 1 indicate that in general, the solvents used in this work are good solvents for these polymers. In the case of PLA/DCM polymer solutions, the concentration range employed gave viscosity values that were a bit outside the recommended range for this type of measurements, so the results presented here have to be used just as an indication, and not as precise values.

Table 1. Viscosity parameters of the studied polymer solutions.

Polymer/solvent	Temperature (°C)	$[\eta]$ (dL g ⁻¹)	k_H	C^* (mg/mL) / wt %
l-PLA / DCM	35	1.30	0.55	7.7 / 0.6
	30	1.54	0.34	6.5 / 0.5
	25	1.66	0.10	6 / 0.45
PLGA / DCM	35	0.42	0.27	24 / 1.8
	30	0.40	0.30	25 / 1.9
	25	0.38	0.32	26 / 2
PLGA / ACE	35	0.30	0.35	34 / 4.3
	30	0.26	0.52	39 / 5
PLGA / ETHY	35	0.32	0.20	31 / 3.5
	25	0.32	0.20	31 / 3.5

The values of C^* obtained indicate that for PLA/DCM solutions, for concentrations above 0.5-0.6 wt%, polymer coils begin to overlap. For the PLGA, the overlap begins at higher concentrations, ~1.8, ~ 4.3 and 3.5 wt % in DCM, ACE and ETHY respectively.

II.2 Precipitation measurements

Results are presented in Table 2, for experiments carried out at 313 K and with a 100 μ m nozzle diameter.

These results showed that for PLA, at a concentration of 1 wt%, a fine powder was obtained. Increasing the concentration to 2 and 3 wt% lead to the formation of fibres, and a mixture of fibres and powder was recovered. SEM pictures allowed to determine that the fibres are composed of flocculated microspheres. For all the experiments, primary particles sizes were almost the same. Concentration of these solutions were higher than the C^* values determined from the viscosity measurements. When working at concentrations higher than C^* , we can expect that chain entanglement and increased solution viscosity will influence the morphology, and thus fibres could be obtained. Even though polymer concentration in runs 1 and 2 was higher than C^* , a fine powder was obtained. Thus, as already remarked by Luna-Barcenas et al. [4] for polyacrylonitrile in dimethylformamide, it appears that phase

separation took place at a point where C^* was intermediate between the good-solvent and Θ -solvent limits.

Table 2. Morphologies obtained by spraying a polymer solution into CO_2 at 313 K.

<i>Run / Polymer Concentration (wt%)</i>	<i>Solution flow rate (mL/min)</i>	<i>CO₂ flow rate (mL/min)</i>	<i>Macrostructure</i>	<i>Microstructure (SEM)</i>
<i>l-PLA, P = 11 MPa, solvent : methylene chloride</i>				
1 / 1	0.5	7	fine powder	microspheres
2 / 1	0.5	67	fine powder	microspheres
3 / 2	3	67	powder + small fibre bundles	flocculated + non flocculated microspheres
4 / 3	0.9	67	fibre bundles + few powder	Flocculated + non flocculated microspheres
5 / 3	3	67	powder + fibre bundles	microspheres + fibers
6 / 3	6.3	67	fibre bundles + few powder	Flocculated microspheres that form highly oriented microfibrils
<i>PLGA (50 :50) + solid solute, P =8.5 MPa, solvent : methylene chloride</i>				
7 / 2.4	3.4	67	Cotton-like material	Rods coated by a sinusoidal film
8 / 1.2	3.2	67	Compact cotton-like material	Rods coated by a sinusoidal film
9 / 0.8	3.2	67	Compact cotton-like material	Rods
10 / 0.6	3.2	67	Cotton-like material	Rods coated by a sinusoidal film
11 / 0.3	3.3	67	Cotton-like material	Rods coated by a sinusoidal film
<i>PLGA (50 :50) + solid solute, P =8.5 MPa, solvent : acetone</i>				
12 / 3.2	3.3	67	Airy cotton-like material	Rods coated by an irregular film
<i>PLGA (50 :50) + solid solute, P =8.5 MPa, solvent : ethyl acetate</i>				
13 / 0.9	3.3	67	Airy cotton-like material	Rods coated by a sinusoidal film

Precipitation of a pure PLGA solution was also realised, but it was found that this polymer only formed a film that coated the internal walls of the vessel, and no free particles were collected. For this reason, the precipitations were carried out from solutions containing PLGA + a solid solute. The results showed that the polymer coated the solute, and from SEM pictures it could be seen that when using DCM, ACE or ETHY, the coating presented a sinusoidal form. Whatever the experimental conditions and solvent, the macrostructure of the material recovered was almost the same. The main difference was on the width of the coating on the rods, which seemed higher for run 2 than for the others.

II.3 Dimensionless numbers calculation

To characterize these experiments, the dimensionless Reynolds (Re) and Weber (We) numbers for the studied solutions were calculated, and are shown in Table 3. The We is the ratio of the inertial forces to surface tension forces and is given by $We = \rho_A v^2 D / \gamma$ where ρ_A is the antisolvent density, v is the velocity of the jet relative to that of the CO_2 , D is the solution

jet diameter, and γ is the interfacial tension [10]. Because γ between the polymer solution and CO₂ is unknown, We numbers are normalized by another value, assuming γ is constant.

It can be seen that for PLA experiments, a poor mixing outside of the jet can be expected due to a small Re of the solution, and a laminar CO₂ flow. These conditions slow mass transfer in the suspension outside the jet, and may have an impact on particles flocculation and agglomeration.

For the PLGA experiments, higher solution Re are obtained - due to a smaller viscosity of the PLGA solutions - , but the CO₂ flow is still laminar.

Table 3. Effect of experimental parameters on Re and We numbers, for polymer solutions sprayed through a 100 μm nozzle diameter, into CO₂ at 313 K and flowing at 67 mL/min.

Run	u _{liquid solution} (m/s)	Re solution	Re CO ₂	We /We(run 2)	We /We(run 6)	We /We(run 3)	We /We(run 10)
<u>PLA/DCM</u>							
1 ^a	0.9	111	54	2.2	0.05	0.02	
2	1.2	142	548	1	0.002	0.01	
3	6.4	318	221	97	0.2	1	
4	1.8	44	110	4.4	0.01	0.05	
5	6.2	150	110	90	0.2	0.93	
6	13.4	326	105	470	1	4.9	
<u>PLGA/DCM</u>							
7	6.6	858	332				1,1
8	6.2	1298	568				0,93
9	6.5	1613	665				1,1
10	6.4	1687	671				1,0
11	6.3	1842	742				0,97
<u>PLGA/ACE</u>							
12	6.4	979	736				0.93 ^b
<u>PLGA/ETHY</u>							
13	6.4	1304	687				0.94 ^c

^a CO₂ flow rate of 7 mL/min

^b We/We(run7)

^c We/We(run9)

For PLGA experiments, We numbers are almost the same. In fact, the solution and CO₂ flow rates were maintained at the same values, and only the concentration was changed. Increasing the concentration by a factor of 8, only lead to a viscosity increase of 2.2. So, no important variations were obtained on the We number.

On the contrary, for PLA solutions, increasing the polymer concentration by a factor of 3, gave a viscosity 5 times higher. The We numbers present in this case some differences, particularly when normalized by the value of run 2. Liquid atomization theory predicts finer atomization and smaller droplet sizes with increasing We numbers. Thus, in the SAS processes, smaller polymer particles should be obtained at higher We numbers. According to this, runs 3 to 6 should have lead to the formation of smaller particles, but as stated before, this was not the case. The We number based analysis of jet break up ignores the viscous forces resulting from the continuous phase. However, at some point, this viscosity terms can no longer be neglected, and the We number in no longer the appropriate parameter to characterize dispersion in this systems [3].

Under the conditions used in this work, the solvent is fully miscible with the compressed CO₂. Thus static equilibrium surface tensions between the jet and the antisolvent are near zero. Lengsfeld et al.[3] found that the distance from the nozzle, at which the surface tension approaches values near zero, for a 10 cm/s methylene chloride jet in 8.5 MPa, 35°C

carbon dioxide was 1 μ m. This distance is shorter than the characteristic breakup lengths, so distinct droplets never form. A dilute concentration is necessary for this, because as polymer concentration increases a third species will begin to influence the phase behaviour of the system and to sustain surface tension.

Dukhin et al.[11] published some results regarding the dynamic interfacial tension (DIT) for an ethanol-CO₂ mixture at high pressures. They have shown that, for a pressure far above the critical point of the mixture (CPM), a fibre-like and helical threads emerged from the nozzle, and quickly dissolved into the supercritical CO₂/ethanol media. Neither droplets nor well-defined jet boundaries were observed. On the contrary, for pressures slightly above the CPM, they found evidence of a transient existence of droplets, and the jet flow patterns indicate the existence of a DIT.

The PLA precipitation experiments were carried out at a pressure above the CPM. Fibre formation is certainly due to the high viscosity of the polymer solutions, associated to the flow patterns described by Dukhin et al.[11]. The existence of a poor mixing outside the jet is indicated by the low *Re* numbers, but the results (runs 1 and 2) showed that more than mixing, it is the concentration and thus the viscosity that plays an important role in the morphology of the product.

In the case of PLGA, the pressure was just slightly above the CPM. At these conditions, a DIT may exist. The coating of the solute by a sinusoidal film is in accordance with the existence of droplets and the jet flow pattern indicated by Dukhin et al.[11].

ACKNOWLEDGEMENTS

Acknowledgement is made to the European Commission (Contract NMP2-CT-2005-013524) for financial support. Also, the authors want to thank Mr Patrick Portes for the samples SEM analysis.

REFERENCES

- [1] DIXON, D. J., JOHNSTON, K. P., BODMEIER, R. A., *AIChE*, Vol. 39, **1993**, p. 127.
- [2] RANDOLPH, T. W., RANDOLPH, A. D., MEBES, M. YEUNG, S., *Biotechnol. Prog.*, Vol. 9, **1993**, p. 429.
- [3] LENGSELD, C. S., DELPLANQUE, J. P., BAROCAS, V. H., RANDOLPH, T. W., *J. Phys. Chem.*, Vol. 104, **2000**, p. 2725.
- [4] LUNA-BARCENAS, G., KANAKIA, S. K., SANCHEZ, I. C., JOHNSTON, K. P., *Polymer*, Vol. 36, **1995**, p. 3173.
- [5] PEREZ de DIEGO, Y., PELLIKAAN, H. C., WUBBOLTS, F. E., WITKAMP, G. J., JANSSENS, P. J., *J. Supercrit. Fluids*, Vol. 35, **2005**, p. 147.
- [6] BILLMEYER, F. W. Jr, *Textbook of Polymer Science*, Wiley-Interscience Publication, New York, **1971**.
- [7] VEGA-GONZALEZ, A., DOMINGO, C., ELVIRA, C., SUBRA, P., *J. Appl Polym Sci*, Vol. 91, **2004**, p. 2422.
- [8] YDENS, I., MOINS, S., DEGEE, P., DUBOIS, P., *Eur Polym J*, Vol. 41, **2005**, p. 1502.
- [9] FONTANILLE, M., GNANOU, Y., *Chimie et physico-chimie des polymères*, Dunod, Paris, **2002**.
- [10] LEFEBVRE, A. H., *Atomization and sprays*, Hemisphere Publishing Corporation, New York, **1989**.
- [11] DUKHIN, S. S., ZHU, C., DAVE, R., PFEFFER, R., LUO, J. J., CHAVEZ, F., SHEN, Y., *Colloid Surface*, Vol. 229, **2003**, p. 181.