Experimental Report

02/01/2014

Proposal:	**DIR-109**	**Council:**	10/2012

Title: Kinetic characterization of demixing processes in casting solutions during industrial manufacture of macroporous membranes using SANS

This proposal is a new proposal

Researh Area: Soft condensed matter

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Samples:
C_2D_5OH
CD_2Cl_2

Instrument	Req. Days	All. Days	From	To
D11	2	2	03/07/2013	05/07/2013

Abstract:

Kinetic characterization of demixing processes in casting solutions during industrial manufacture of macroporous membranes using SANS

Introduction

The use of macroporous membranes for the production of biopharmaceuticals massively increases since the development of single use devices [1]. Such membranes are now used all along the biopharmaceutical process from the media preparation to the sterile filtration of formulated vaccines via cell harvesting, protein purification and virus removal [2].

All manufacturing processes for such membranes are based on the induced demixing of a homogeneous polymer solution. Demixing phenomena of such solutions are usually induced by temperature changes (quenching). In our case, the demixing is induced by changes in composition meaning that one increases the proportion of non-solvent. Due to the fact that production processes use up to four different components, the situation is rather complicated since several miscibility gaps are formed which tend to overlap.

Small Angle Neutron Scattering (SANS) is a well-known and established tool for the investigation and characterization of demixing phenomena. It enables us to perform time resolved experiments in order to elucidate the mechanisms and the kinetics of the demixing process and its composition dependence at the demixing point. Furthermore, this helps to specify in which range typical control parameters (e.g. composition, temperature, film thickness …) have to be set in order to achieve higher process control and process stability.

Experimental Setup

The experimental setup, which was developed at Sartorius-Stedim GmbH to model industrial equipment, is depicted in the technical form of the proposal. The starting solution consisting of solvent, non-solvent and polymer was prepared and stirred within a remote apparatus. Itself consisting of a reactor, dosing pumps and storage bottles. After a clear and homogenous solution was obtained, addition of non-solvent smoothly induced the demixing of the dope. This solution was continuously pumped through the flow cell placed on the sample table of D11 and through an optical transmission cell which was used to monitor the process. Simultaneous with start of the demixing reaction the time resolved data-acquisition was started. After complete demixing, the solution was regenerated to begin a new cycle. Table 1 and table 2 respectively list the composition of the solutions and the measurement settings which have used during our D11-experimenmts in 2013.

Table 1: Composition of the used solutions

	cellulosenitrate [% (w/w)]	**methyleneacetate** [% (w/w)]	**Isopropanol** [% (w/w)]	**D_2O** [% (w/w)]
Measurement 1	0.0	85.0	2.9	12
Measurement 2	0.6	84.5	2.9	12

Table 2: measurement settings

	D2O	**method of advice**	**time/spectra**	**distance probe/detector**	**wavelength**
Measurement 1	50 mL	impulse	30 sec	39 m	8 nm
Measurement 2	50 mL	impulse	30 sec	39 m	8 nm

The settings of Measurement 1 were used for the investigation of the demixing process in the two phase domain of the ternary mixture of solvent (methyleneacetate) and non-solvents (isopropanol and D2O). In solution 2 we added a polymer to the solution and the demixing process takes place in the overlap region of the miscibility gap of the liquid components (methyleneacetate, isopropanol and D2O) and the gap due to the polymer.

Results

Fig. 2 shows the result of the SANS measurement at the demixing process in the two phase domain of the mentioned ternary mixture of type 1 without any polymer. The scattered intensity abruptly increases with the induction of the demixing process. There are no observable changes of the intensity demixing has been induced. It can be concluded the formed structures are bigger than the range of SANS as result of a fast visual detectable coalition process.

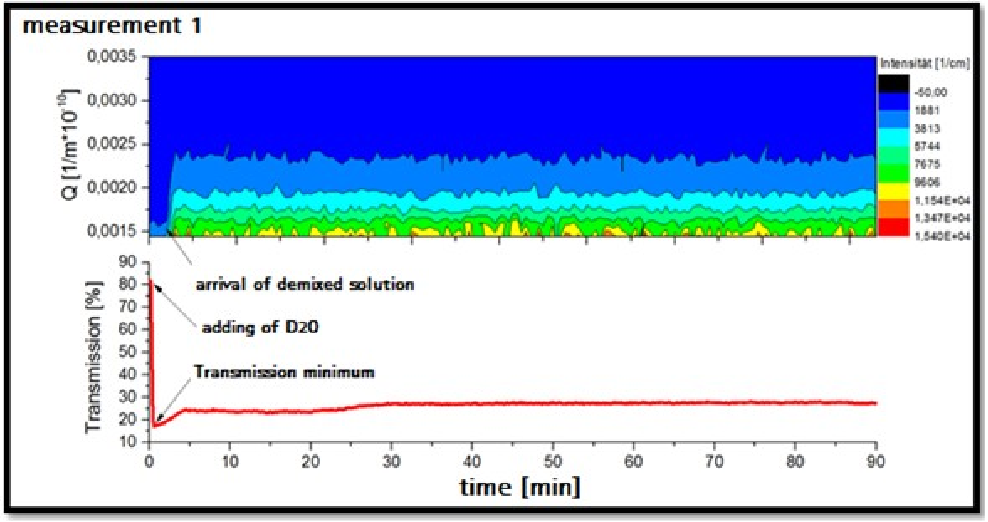

Figure 2: Results of the SANS Measurement 1 compared with the measured transmission.

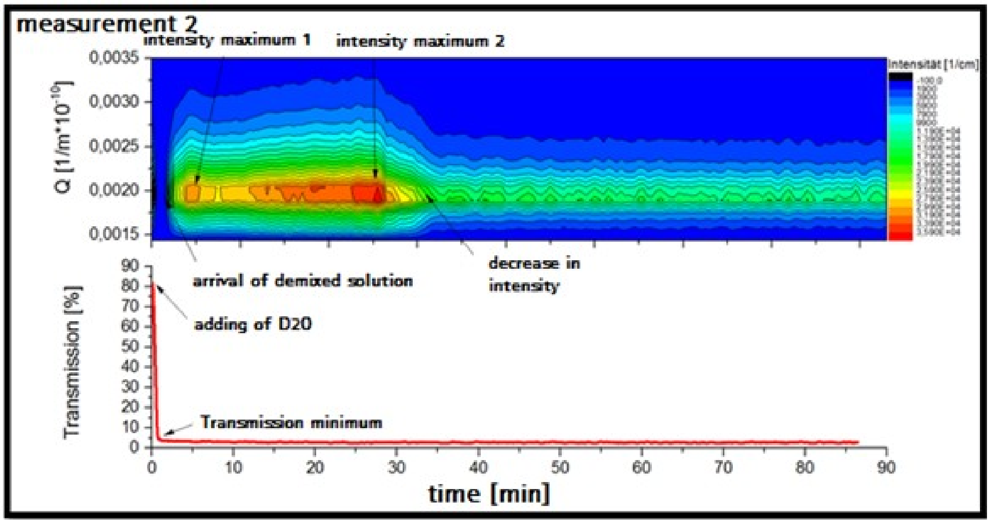

Figure 3: Results of the SANS Measurement 2 compared with the measured transmission

With polymer in the solution of type 2, however, (Fig. 3) a well-defined peak at about 2 10^{-3} $Å^{-1}$ develops which reflects the correlation of precipitates. The time-evolution of the integrated intensity, the Q-Value at maximum intensity (as determined with Furukawa equation [3]) and the calculated distance between the precipitates are displayed in Fig. 4.

The Q-Value is constant from the arrival of the demixed solution in the neutron beam until 25 min. During this time interval, the scattered intensity passes two maxima. After this first period, the Q-Value decreases between 25 and 35 minutes. At the same time, the intensity drops significantly. This period is attributed to coarsening processes. The following mechanism could explain these results: The demixing process starts from a position in the overlap region of two mixing gaps in the four-component system. The fast demixing process associated with the well-defined correlation peak, results from a spinodal demixing process in a D_2O-rich and a methyleneacetate-rich phase. The composition of the equilibrium phase changes the first 25 min and a steady growth of intensity is observed. (The intermediate decrease of the intensity after 5 min may be the result of an H/D-exchange between D_2O and the other components) The subsequent coarsening process and the corresponding decrease of intensity after 25 minutes might be explained by demixing of the methyleneacetate-rich phase into a polymer-rich and a polymer-lean phase.

After having demonstrated that industrial processes can in fact be mimicked by an in-situ set-up and after having obtained first kinetic data, it is obvious that SANS is an extremely powerful tool to gain insight into the microscopic mechanism. The present pilot experiment therefore opens the possibility to explore and to improve the manufacturing process.

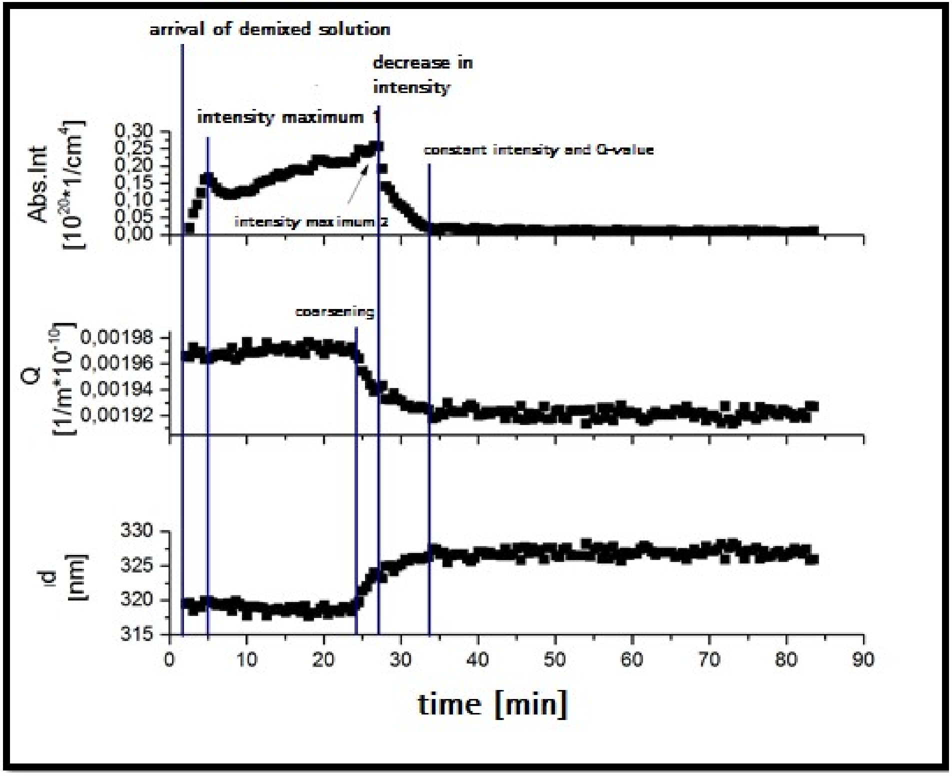

Figure 4: Development of the absolute Intensity, of the Q-Value at maximum Intensity (determined with Furukawa equation [3]) and the calculated distance between the scattering objects

[1]. Z. F. Cui, H.S. Muralidhara *Membrane Technology: a practical guide to membrane technology and applications in food and bioprocessing*. (Butterworth-Heinemann: Burlington, 2010).

[2]. R. Eibl, D. Eibl (eds.), *Single-Use Technology in Biopharmceutical Manufacture*, Wiley-VCH, 2011

[3] H. Furukawa, *Dynamic - Scaling Theory fpr Phase-Seperating Unmixing Mixtures: Growth Rates of Droplets and Scaling Properties of Autocorrelation Functions*. Physika. **1984**, Bd. 123A, S. 497 - 515