Experimental report

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Proposal: 8-03-809 **Council:** 4/2014

Title: SANS investigations on aggregationphenomena in supersaturated drug solutions

Research area: Chemistry

This proposal is a new proposal

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Samples: Iopamidol

Instrument	Requested days	Allocated days	From	To
D11	2	1	29/04/2015	30/04/2015

Abstract:

Non-ionic Iodinated Contrast Media (NICM) are investigative drugs of great relevance in delicate radiological analysis like angiography. The success of these molecules mainly resides in some peculiar physic-chemical properties that associate relatively low-osmolality with low-viscosity up to high concentration in water. NICM are characterized by atropisomerism, a particular chirality due to hindered rotations that gives rise to metastable conformational isomers in solution. The hypothesis is that atropisomeric conformational disorder is stabilized in the molecular aggregation, a phenomenon that inhibits crystallization from supersaturated solutions [5]. Since atropisomers can in principle be equilibrated thermally and NICM solutions are supersaturated, two key factors are identified in temperature and concentration.
We propose to use the D11 diffractometer to investigate as a function of temperature and concentration the behavior of atropisomeric drug molecules in solution that allows stability of supersaturated solutions.

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SANS investigations on aggregation phenomena in supersaturated drug solutions

In the present work the behavior of atropisomeric drug molecules in solution has been investigated by means of small angle neutron scattering (SANS) experiments. The main goal is the characterization of the molecular mechanism that allows stability of supersaturated solutions. The selected molecule is iopamidol (Figure 1), a non ionic iodinated contrast media (NICM), widely used for diagnostic purpose. The main advantage of using this molecular system is that only one enantiomer is present in the commercially available preparation.

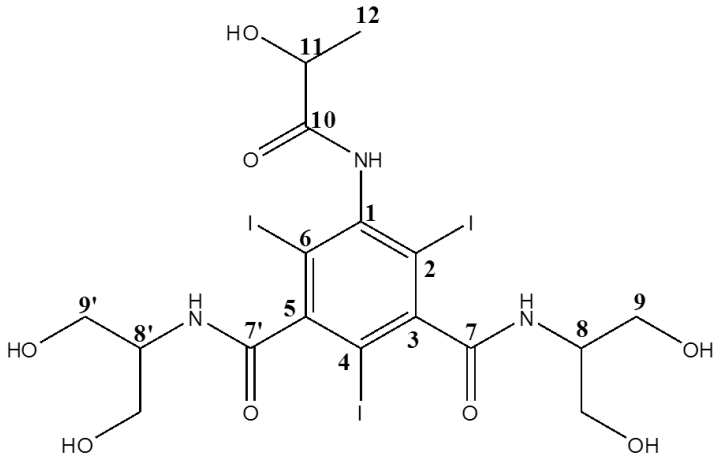

Figure 1 Molecular structure of iopamidol.

SANS experiments were performed on solutions of iopamidol in deuterated water at a concentration of 0.9 mol/kg. Samples were prepared by using two different thermal treatments: after iopamidol powder dissolved in D_2O, the resulting solutions were heated at 80 °C or 110°C for a time interval of 15 minutes or 30 minutes, respectively. In order to evaluate the aging effect on the solution stability, every 7 days, for a total time of 2 months, two samples with the two different thermal treatments were prepared. A total of 16 samples, as well as two diluted solutions were then investigated.

Figure 2 displays the measured scattering intensities of the oldest iopamidol solutions. The two different thermal treatments are reported in Figure 2a (80°C) and Figure 2b (110 °C). Data are compared with iopamidol solution without thermal treatment and with the two samples without aging treated at 80 °C or 110 °C.

Data clearly suggests an evolution over time of the aggregates in solution. Whether this behavior is related only to a size increase or to a change of intermolecular interactions affecting the form of the aggregates has to be clarified. Nonetheless, the important outcome is that for the first time small aggregates of iopamidol were detected.

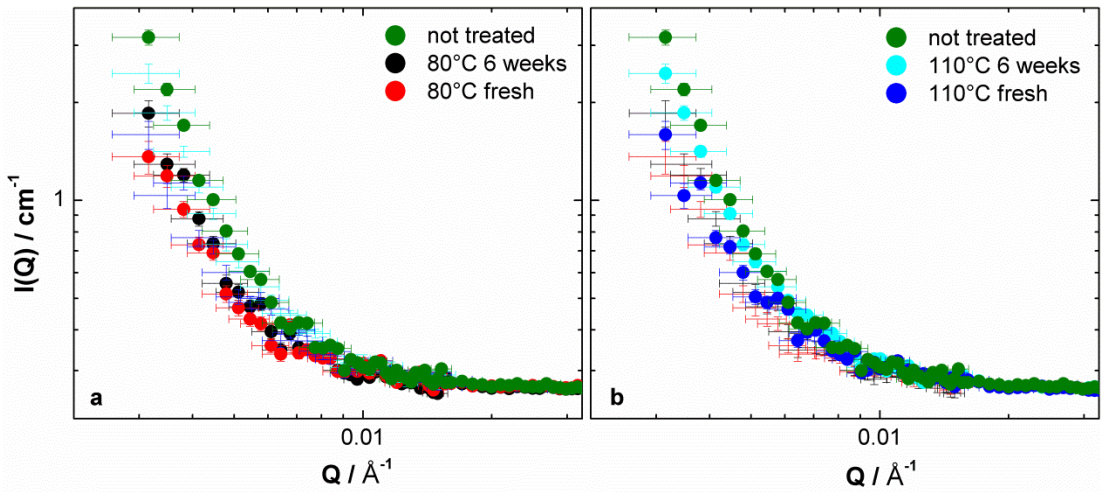

Figure 2 Measured I(Q) of iopamidol solutions in D_2O. a) Samples that have undergone a thermal treatment at 80°C with and without aging b) Samples that have received a thermal treatment at 110°C with and without aging. The measured I(Q) of iopamidol solution in D_2O without thermal treatment is also shown for comparison purpose.

To further characterize the formation of iopamidol aggregates, complementary measurements on the same solutions have been carried out by means of static and dynamic light scattering at the PSCM laboratories.