Effect of hydrophobicity/hydrophilicity balance of thermo-activated solvation mechanism in stimuli-responsive hydrogels based on cyclodextrin

Cettina Bottari[1], Barbara Rossi[1], Francesco D'Amico[1], Alessandro Gessini[1], Lucia Comez[2], Silvia Corezzi[3], Valentina Venuti[4], Vincenza Crupi[4], Domenico Majolino[4], Andrea Mele[5], Lucio Melone[5,6], Carlo Punta[5], Claudio Masciovecchio[1]

1Elettra – Sincrotrone Trieste, Strada Statale 14 km 163.5, Area Science 70 Park, 34149 Trieste, Italy; cettina.bottari@elettra.eu

2 IOM-CNR c/o Dipartimento di Fisica e Geologia, Università di Perugia, via Pascoli, 06123 Perugia, Italy.

3Dipartimento di Fisica e Geologia, Università di Perugia, via Pascoli, 06123 Perugia, Italy

4Dipartimento di Scienze Matematiche e Informatiche, Scienze Fisiche e Scienze della Terra, Università di Messina, V.le F. Stagno D'Alcontres 31, 98166 Messina, Italy.

5 Department of Chemistry, Materials and Chemical Engineering "G. Natta", Politecnico di Milano and INSTM local unit, Piazza L. da Vinci 32, 20133, Milano, Italy

6 Universita` degli Studi e-Campus, Via Isimbardi 10, 22060 Novedrate, Como, Italy

Hydrogels are a class of materials which are particularly useful in many biological and biomedical applications. These systems are more similar to natural soft tissue than any other type of biomaterial for their high water content and biocompatibility. The possibility to vary the chemical composition and the molecular structure of polymer network of hydrogels allows us to extend the use of these systems to tissue engineering, controlled drug delivery and bio-nanotechnology. Environmentally sensitive hydrogels can change their structure and chemical-physical properties in response to external stimuli, such as pH or temperature variations. These characteristics permit the use of hydrogels as smart drug carriers. In particular thermo-responsive hydrogels are capable of changing their physical state in controlled way and *in situ*. For example, the changing of temperature due to their injection into physiological environments provides the advantage of more targeted and convenient administration of bioactive agents, such as in chemotherapy drugs. In a similar way there are hydrogels that change their physical-chemical properties in response to pH value. Besides these practical aspects, hydrogels materials allow to understand how the behaviour of water in the proximity of hydrophobic and hydrophilic groups of complex molecules can drive gelation phenomena. In this contest cyclodextrin nanosponges (CDNS) represent a new delivery system which allow a tuning of the therapeutic demands of the pathology, with the presence of both hydrogen-bond donor/acceptor groups in the polymeric backbone of the hydrogel matrix [1]. They offer interesting possibilities to encapsulate both hydrophobic and hydrophilic active ingredients. In particular, the formation of CDNS hydrogels is possible by swelling the polymer in an aqueous solution of a given bioactive compound of interest.

In this framework, we approached the study of the thermosensitive behaviour exhibited by pH-responsive cyclodextrin-based hydrogels by the joint use of UV Raman scattering, IR and Brillouin spectroscopy to monitor the phase changes in polysaccharide hydrogel materials and their influence on the localized and collective vibrational dynamics of the system. We combined the information that can be extracted by exploiting the use of complementary vibrational spectroscopic techniques (UV Raman and IR spectroscopy) to investigate how macroscopic properties, like the gelling behaviour of CDNS hydrogels, change according to the tuning of the covalent cross-linking degree and the hydrophobicity/hydrophilicity balance. Again, the mechanism of thermo-activated solvation plays an important role in the swelling ability of the final product. This mechanism is well described by the so-called activation temperature T^* that is defined as the characteristic temperature at which we observe a significant decreasing of the dephasing time τ_{deph} associated to the vibrational modes of specific chemical moieties present in the CDNS polymer structure. This activation temperature T^* has been observed to be strongly dependent on the pH conditions of hydration of polymers [2]. In a complementary way, Brillouin scattering is used to probe the collective dynamics of the system, by measuring the propagation velocity and the attenuation of longitudinal acoustic modes at different conditions of temperature and pH. In particular, we observed a decrease of Brillouin peak frequency upon increasing of temperature; as main result, we found that the phase transition temperature strictly depends on pH value, covalent cross-linking degree and hydrophobicity/hydrophilicity balance in CDNS.

All the results presented here corroborate the importance of the joint use of different vibrational technique in order to have a complete comprehension of the molecular structure and behavior of complex system like CDNS hydrogels.

References

[1] V. Crupi, et al., *Soft Matter*, **10**, 2320 (2014)

[2] B. Rossi et al., *Soft Matter*, **11**, 5862 (2015)