

Photostability of therapeutic monoclonal antibodies (mAbs) in their formulation and sterile saline or glucose solutions for parenteral administration within a chemical surface tensiometry combined approach.

Giorgia Miolo, Elisabetta De Diana, Patrizia Polverino de Laureto and Davide Rossi
Department of Pharmaceutical and Pharmacological Sciences, Via F. Marzolo 5, Padova,
University of Padova, Italy

Monoclonal antibodies (mAbs) are complex protein molecules, and their structural integrity impacts on their biological and pharmacological activity, i.e., against cancer and pathogens. Handling protein pharmaceuticals still presents challenges that need to be addressed to generate further evidence on their stability and, therefore, safety, efficacy, and immunogenicity.

We investigated the impact of some stress factors, i.e., shaking/vibrations, temperature, dilution and light exposure, on the formulated anticancer monoclonal antibody Nivolumab (Opdivo®) with or without dilution (saline and glucose solutions) trying to mimic the routine handling once released from the pharma industry, shipped to the hospital, diluted for the parenteral administration, and finally administered to the patients.

mAb stability analyses, including aggregation and dilution effects on the protein structure, were carried out by biochemical (SEC, size exclusion chromatography, SDS-PAGE, and fingerprinting) and biophysical (Uv-Vis, fluorescence, circular dichroism, CD) methods but an approach through surface tensiometry analyses was added to get new information. Indeed, a new concept of Integrated Analytical Approach was applied to the study of solid and liquid complex systems, based on the integration between the data obtained from different analytical fields performing on the same sample and at the same time. The surface tensiometry analyses were performed using the contact angle (CA) method, and the Solid-like methodology (SLM), a procedure capable to determine the CA at the interface between the liquid samples and a liquid film of Fomblin HC/25™ PFPE (PFPEf) as solid substrate without the influence of s/l interfacial friction forces and roughness surface. The application of SLM to the study of mAbs, led us to determine the Surface Tension (ST: mN/m), Dispersive Component (DC: mN/m), and Polar Component (PC: mN/m) using the Rossi number (χ_{PFPEf}^L) a pure number capable to reveal the ST and the energy variations of a liquid systems. In the end, surface tensiometry and biochemical/biophysical data were compared and correlated each-others.

A critical exogenous stressing factor that was particularly taken in consideration is indoor and outdoor light exposure to which a drug product could be exposed during the transport or within the hospital and even during the time of administration to the patient.

Nivolumab showed to be quite stable under vigorous shaking and moderate temperature (37°C) for 45 days. However, it undergoes structural change, mostly aggregation and AA oxidation, upon exposure to artificial sunlight. The dilution media used for administration to the patients, in particular the sterilized glucose solution containing degradation glucose products, i.e., HMF, should be considered in terms of photostability of the drug product. Moreover, we could detect a protein modification in the dark when dilution in glucose was compared to that in saline or non-sterile glucose.

The instability of mAbs in sterile glucose solution and/or upon light exposure could have a potential impact on the safety and efficacy of these very active drugs in the anticancer therapy.