AGING EFFECT ON THE PHASE TRANSITION AND DRUG RELEASE PROPERTIES OF POLY(N-ISOPROPYLACRYLAMIDE)

Camille Mathieu[a,b] ; Emmanuel Richaud[b] and Samar Issa*[a]

[a] *Ecole de Biologie Industrielle - EBI, UPR EBInnov®, 49 Avenue des Genottes CS90009 95895, Cergy-Pontoise, France*

[b] *Laboratoire PIMM, Arts et Métiers Institute of Technology, CNRS, Cnam, HESAM Université, 151 boulevard de l'Hôpital, 75013 Paris, France*

*s.issa@ebi-edu.com

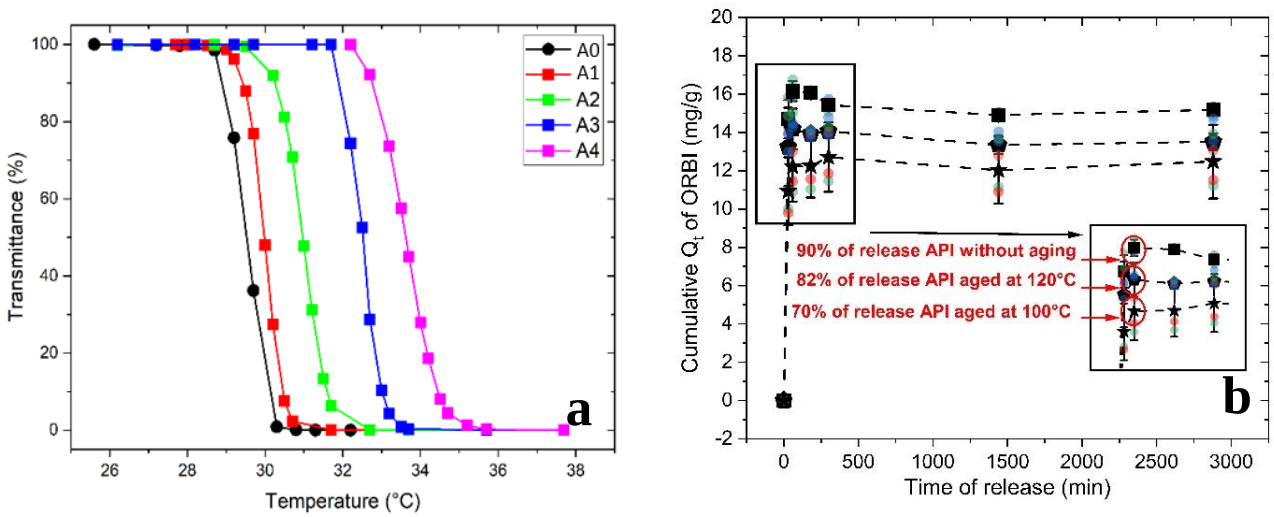
Mots-clés : poly(N-isopropylacrylamide), aging, phase transition temperature, hydrogel, drug release

Résumé :

Aqueous solutions of poly(N-isopropylacrylamide)-based polymers (PNIPAm) are commonly studied due to their lower critical solution temperature (LCST) around 25-35°C [1] close to body's temperature. These smart polymers demonstrated interest in biomedical application such as stimuli-sensitive excipients for drug delivery systems [2]. In water, the thermoresponsive behavior is related to the equilibrium between hydrophobic (isopropyl) and hydrophilic (amide) groups associations with water molecules [1]. At temperature lower than LCST, amide groups are linked to water molecules through Hydrogen bonds (H-bonds). Upon heating, H-bonds are broken, and hydrophobic interactions dominate resulting in the collapse of polymeric chains. The mechanism of phase separation has been successfully investigated since 1968 [3]. With increased research in pharmaceutical applications, it is quite interesting to explore the thermal and chemical stability of these polymers. The purpose of this study is to explore the stability under thermal and longtime aging (at 120°C and 100°C). The modification of phase separation followed by a turbidity method is described as well as the attempt to better understand the possible mechanisms underlying the observed alterations. The impact of aging on drug release is revealed and correlated to molecular and macromolecular changes. Commercially available linear PNIPAm (535311, Sigma-Aldrich) (Mn = 40 $kg.mol^{-1}$) and synthesized hydrogel [4] were used for the release of antibiotics (orbifloxacine, Y0001125, Sigma-Aldrich).

The phase transition temperature (T_{cp}) of PNIPAm solutions (with PNIPAm weight ratio at 0.01) was determined based on turbidity with a UV-Spectrometer (UV-Vis Lambda 35, Perkin Elmer) equipped with heating device. The utilized wavelength was 651nm and the heating rate was 0.3°$C.min^{-1}$. Drug release of orbifloxacin, used as a model drug (BCS Class IV), is performed in a dialysis membrane bag in 20mL of PBS. Amounts of orbifloxacin are determined by UV-VIS at an absorbance of 282nm. Aging modifications are investigated only on linear PNIPAm which appears to be a simpler model similar to cross-linked PNIPAm. Average molecular weight (Mw) estimation was determined by Gel Permeation Chromatography (GPC) (OMNISEC, Malvern, Columns T3000 – T6000) using 2$mg.mL^{-1}$ in tetrahydrofuran. Spectra of solid polymer samples were collected on a Fourier Transform Infrared (FTIR Frontier, Perkin Elmer) within a range of 4000-650cm^{-1} by averaging 32 scans, with a wavenumber resolution of 4cm^{-1}. Sorption samples were analyzed at a constant temperature of 40°C. Samples were obtained by casting PNIPAm solutions in a jar. The relative humidity (RH) increased from 0% to 90% (in 5% steps). The stage time between steps was 3 hours.

After an initial aging study, a variation in T_{cp} of a few degrees is demonstrated, up to 4°C. Furyk and al. [5] showed that turbidity curves are very sensitive to the molecular weight (Mw) and group interactions with water molecules, for PNIPAm with Mw lower than 20$kg.mol^{-1}$. Variations in thermosensitive behavior appear to be governed mainly by variations in Mw [6]. Aging generated chain scissions, for example after 90 days at 120°C, Mw decreased by 50% accompanied with the formation of more hydrophilic oxidized species, with -C=O functions detected with FTIR. These new species enabled intra- and inter-chain polymer-polymer interaction resulting in increase in glass temperature (T_g) with aging. Moreover, after aging, sorption isotherms showed a slightly more hydrophilic profile than in the initial state. The maximum volume fraction increased from 15.7% before aging to 17.9% after 90 days at 120°C. These modifications with aging directly altered drug release property. Indeed, with a decrease of Mw burst release effect is clearly extended. However, with the introduction of new oxidized species and an increase of hydrophilic species, the total amount at the plateau is reduced and the PNIPAm entrapped more orbifloxacin.



a) Turbidity curves (at 1% in weight fraction polymer solution) comparing unaged (A0) vs. aged samples at 120°C: (A1:30-days, A2:60-days, A3:90-days and A4:120-days aging); b) Drug release curves of orbifloxacin (API:active pharmaceutical ingredient) at 37°C comparing unaged (■) vs. aged 2 months at 100°C (★) and 120°C (⬟)

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