

TEMPERATURE/pH DUAL STIMULI-RESPONSIVE COPOLYMERIC NANOHYDROGELS. SYNTHESIS, CHARACTERIZATION, PROPERTIES AND NANOMEDICINE APPLICATIONS

Issa Katime¹, Aintzane Asumendi², Arturo Álvarez-Bautista¹, María D. Boyano³, Saira Hernández Olmos¹, Erika Alonso-Tejerina², Teresa G. Granda³, María D. Blanco⁴

¹Grupo de Nuevos Materiales y Espectroscopia Supramolecular, Facultad de Ciencia y Tecnología, UPV/EHU. Instituto de Investigación Sanitaria BioCruces. Vizcaya, Spain. Email: issa.katime@ehu.es

²Departamento de Biología Celular e Histología, Facultad de Medicina y Odontología UPV/EHU

³Instituto de Investigación Sanitaria BioCruces, Vizcaya, Spain.

⁴Departamento de Bioquímica. Facultad de Medicina. Universidad Complutense de Madrid, Spain.

Cancer is a disease caused by a group of cells that grow and multiply themselves uncontrollably independently, locally and remotely invading other tissues. Currently there is an urgent need for the use of new forms of administering therapeutic drugs for its treatment, focusing on the ability of the drug to distinguish tumor cells from the healthy ones.

New methods for the release of drugs have been developed to provide better dosing and pharmacokinetic profile and even the reduction of adverse effects. According to the Royal Spanish Pharmacopoeia, this new forms of modified methods are administrated intravenously but are based on the located release of the active substance, minimizing the dosage in comparison with the methodologies used before.

In this context smart nano-hydrogels seem to be a promising approach taking into account the collapsing and swelling properties of the polymers. This is particularly interesting in the case of hydrogels containing poly(N-isopropylacrylamide), which generate matrices that can exhibit thermally reversible collapse above the lower critical point temperature of the homopolymer (≈ 32 °C) and containing also comonomers which exhibit pH responsive changes as 1-vinyl imidazole, acrylic acid and 2-(diethylamino) ethyl methacrylate.

To avoid post-polymerization modification, functionalized monomers able to respond to pH and temperature changes were polymerized. The synthesized monomers have the capability for coupling with folic acid which is the target molecule. For this reason their polymers can be used as targeted drug delivery systems. Smart polymeric nanoparticles were prepared by direct and inverse microemulsion polymerization of the synthesized monomers. The polymerization reaction was performed in presence of an oil-soluble salt to reduce the dimensions of the micellar diameter. The average particle diameter and the particle size distribution of the nanogels were measured in water, at 25 °C, by quasielastic light scattering (QLS) showing an average diameter of 33 nm. The nanogels were studied by FTIR-ATR, ¹H NMR, UV-Vis spectroscopy and DSC. The nanoparticles were charged with drugs and their release kinetic was studied.

Moreover, if an appropriate co-suitable monomer is incorporated, these systems could also have a pre-designed response at different values of pH, releasing the drug selectively; this could be achieved by introducing a pH sensitive monomer in the polymeric core such as 1-vinylimidazole (VMDZ) and acrylic acid or 2-(diethylamino) ethyl methacrylate. Another feature of those intelligent materials is their ability to reach a specific target (cancer cells). As the cancer cells over express folate receptors nanohydrogels are usually functionalized with folic acid so as the receptor-ligand complex can be formed in the cell membrane, enabling an endocytosis process mediated by receptor. We present a synthesis for the poly(NIPA-co-VMDZ) and 2-(diethylamino) ethyl methacrylate which detects pH difference making possible the release of the drug at the theoretical temperature of cancer cells.

In this work the synthesis of smart nanoparticles capable of responding to external stimulus (pH and temperature variations) is reported. To avoid post-polymerization modification, functionalized monomers able to respond to pH and temperature changes were polymerized. The synthesized monomers have the capability for coupling with folic acid which is the target molecule. For this reason their polymers can be used as targeted drug delivery systems. These nanoparticles had shown a selective swelling-collapse response to external pH changes. The nanoparticles were charged with drugs and their release kinetic was studied.

References

1. Antonietti M., Bremser W. *Macromolecules*, **23** (1990) 3796–3805
2. Aguiar A., González-Villegas S., Rabelero M., Mendizábal E., Domínguez J. M., Katime I., *Macromolecules*, **32(20)** (1999) 6767–6771
3. Rabelero M., Zacarias M., Mendizábal E., Puig E., Domínguez J.M., Katime I., *Polym. Bull.*, **38(6)** (1997) 695–700.
4. Guerrero-Ramírez L.G., Nuño-Donlucas S.M., Cesteros L.C., Katime I., *Mater. Chem. Phys.*, **112** (2008)1088–1092
5. Blanco M.D., Guerrero S., Benito M., Fernández A., Teijón C., Olmo R., Katime I., Teijón J.M., *Polymers*, **3(3)** (2011)1107–1125
6. Blanco M.D., Guerrero S., Teijón C., Olmo R., Pastrana L., Katime I., Teijón J.M., *Polym. Int.*, **57**, 1215–1225 (2008).
7. Guerrero-Ramírez L.G., Nuño-Donlucas S.M., Cesteros L.C., Katime I., *J. Phys. Conference Series*, **127** (2008)12010.
8. Katime I., Guerrero L.G., Mendizábal E. “Size Matters: Smart copolymeric nanohydrogels: Synthesis and applications”, in *Frontiers in Bioscience*, E4, 1314–1334 (2012) in “Polymer base nanomaterials for biomedical applications”. P. Taboada and V. Mosquera (Editors).