A New Methodology to Create Polymeric Nanocarriers Containing Hydrophilic Low Molecular-Weight Drugs: A Green Strategy Providing a Very High Drug Loading

Villamizar-Sarmiento, María Gabriela

Molina-Soto, Elton F.

Guerrero, Juan

Shibue, Toshimichi

Nishide, Hiroyuki

Moreno-Villoslada, Ignacio

Oyarzun-Ampuero, Felipe A.

To date, a large number of active molecules are hydrophilic and aromatic low molecular-weight drugs (HALMD). Unfortunately, the low capacity of these molecules to interact with excipients and the fast release when a formulation containing them is exposed to biological media jeopardize the elaboration of drug delivery systems by using noncovalent interactions. In this work, a new, green, and highly efficient methodology to noncovalently attach HALMD to hydrophilic aromatic polymers to create nanocarriers is presented. The proposed method is simple and consists in mixing an aqueous solution containing HALMD (model drugs: imipramine, amitriptyline, or cyclobenzaprine) with another aqueous solution containing the aromatic polymer [model polymer: poly(sodium 4-styrenesulfonate) (PSS)]. NMR experiments demonstrate strong chemical shifting of HALMD aromatic rings when interacting with PSS, evidencing aromatic-aromatic interactions. Ion pair formation and aggregation produce the collapse of the system in the form of nanoparticles. The obtained nanocarriers are spheroidal, their size ranging between 120 and 170 nm, and possess low polydispersity (?0.2) and negative zeta potential (from -60 to -80 mV); conversely, the absence of the aromatic group in the polymer does not allow the formation of nanostructures. Importantly, in addition to high drug association efficiencies (?90%), the formed nanocarriers show drug loading values never evidenced for other systems comprising HALMD, reaching ?50%. Diafiltration and

stopped flow experiments evidenced kinetic drug entrapment governed by molecular rearrangements. Importantly, the nanocarriers are stable in suspension for at least 18 days and are also stable when exposed to different high ionic strength, pH, and temperature values. Finally, they are transformable to a reconstitutable dry powder without losing their original characteristics. Considering the large quantity of HALMD with importance in therapeutics and the simplicity of the presented strategy, we envisage these results as the basis to elaborate a number of drug delivery systems with applications in different pathologies.