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A novel *in situ* hydrophobic ion paring (HIP) formulation strategy for clinical product selection of a nanoparticle drug delivery system

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Abstract

The present studies were aimed at formulating AZD2811-loaded polylactic acid–polyethylene glycol (PLA-PEG) nanoparticles with adjustable release rates without altering the chemical structures of the polymer or active pharmaceutical ingredient (API). This was accomplished through the use of a hydrophobic ion pairing approach. A series of AZD2811-containing nanoparticles with a variety of hydrophobic counterions including oleic acid, 1-hydroxy-2-naphthoic acid, cholic acid, deoxycholic acid, dioctylsulfosuccinic acid, and pamoic acid are described. The hydrophobicity of AZD2811 was increased through formation of ion pairs with these hydrophobic counterions, producing nanoparticles with exceptionally high drug loading—up to five fold higher encapsulation efficiency and drug loading compared to nanoparticles made without hydrophobic ion pairs. Furthermore, the rate at which the drug was released from the nanoparticles could be controlled by employing counterions with various hydrophobicities and structures, resulting in release half-lives ranging from about 2 to 120 hours using the same polymer, nanoparticle size, and nanoemulsion process. Process recipe variables affecting drug load and release rate were identified, including pH and molarity of quench buffer.

Ion pair formation between AZD2811 and pamoic acid as a model counterion was investigated using solubility enhancement as well as nuclear magnetic resonance spectroscopy to demonstrate solution-state interactions. Further evidence for an ion pairing mechanism of controlled release was provided through the measurement of API and counterion release profiles using high-performance liquid chromatography, which had stoichiometric relationships. Finally, Raman spectra of an AZD2811–pamoate salt compared well with those of the formulated nanoparticles, while single components (AZD2811, pamoic acid) alone did not.

A library of AZD2811 batches was created for analytical and preclinical characterization. Dramatically improved preclinical efficacy and tolerability data were generated for the pamoic acid lead formulation, which has been selected for evaluation in a Phase 1 clinical trial (ClinicalTrials.gov Identifier NCT 02579226). This work clearly demonstrates the importance of assessing a wide range of drug release rates during formulation screening as a critical step for new drug product development, and how utilizing hydrophobic ion pairing enabled this promising nanoparticle formulation to proceed into clinical development.