Probe into the Physical Properties of a Gelucire® 44/14 Pharmaceutical Formulation

H. Elmaleh , C.Neves , M.-A.Perrin

Aventis Pharma, 13 quai Jules Guesde, 94403 Vitry sur Seine, France

The number of poorly bioavailable drugs developed by the pharmaceutical industry has considerably increased during the last few years. Different approaches to overcoming the problem are currently being used. One way is to disperse the drug substance (DS) in a surface-active carrier in order to enhance its bioavailability; this is commonly called solid dispersion. This study will address the physical characterization of a Gelucire®-based solid dispersion formulation and illustrate some of its potential drawbacks in terms of DS physical stability.

Gelucire® 44/14 is a semi-solid excipient frequently used in the pharmaceutical industry. It is a mixture of glycerol and PEG1500 esters of long fatty acids. The suffixes 44 and 14 refer respectively to its melting point and its hydrophilic/lypophilic balance (HLB). A conventional manufacturing process consists in melting Gelucire® at 60°C and then incorporating the DS. The mixture is then homogenized and poured into gelatin capsules.

The DS used here is a well-crystallized monohydrate, denoted form A. As it dehydrates at 90°C, this crystalline form's thermal stability makes it suitable for a Gelucire® formulation. Nevertheless, attempts to manufacture this formulation failed. When the DS was incorporated into the liquid Gelucire®, there was a rapid increase in the viscosity of the mixture, leading to complete solidification, which made it impossible to pour the preparation into the capsules. Decreasing the operating temperature and/or the DS concentration to optimize the process did not solve the problem. In order to account for this phenomenon, a physical characterization of both the mixture and its individual components was carried out using X-ray powder diffraction (XRPD), high temperature XRPD, differential scanning calorimetry (DSC), hot stage microscopy (HSM) and water sorption/desorption.

It is a particular combination of the physico-chemical characteristics of form A and Gelucire® that caused the formulation process to fail. Gelucire® is highly hygroscopic under high-temperature conditions. Form A dissolves immediately in water, and a few minutes later the solution gels completely. Studies using microscopy and XRPD revealed that gelling proceeds from the hair-like morphology recrystallization into a new crystalline form of DS (a dihydrate), denoted form B. Thus, when form A is incorporated into liquid Gelucire®, a fraction of it dissolves in the water taken up by the Gelucire®, subsequently crystallizing into hair-like crystals (form B) and causing the heated mixture to gel.

During the manufacturing process, the heating & cooling rates, holding time at high temperature, the presence of water in the carrier, and the mechanical stirring can all induce important physical transformations of the DS crystals, such as solubilization, hydration/dehydration, phase transition, recrystallization…. As in-process physical monitoring is very difficult to perform, analysis is usually done at the end of the manufacturing process. Therefore, information concerning the evolution of the physical state of the DS in situ is generally inaccessible. Investigation of the physical state of the DS in the formulated product during processing and its stability over time still remains a major challenge.