Empirical model-based identification of critical quality attributes in the preclinical design of nanostructured lipid carriers
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T. Bastogne1,2,3, J. Bruniaux4,5,6,7, F. De Crécy4, F. Navarro4,
1Centre de Recherche en Automatique de Nancy (CRAN), Université de Lorraine, CNRS~UMR~7039, BP 70239, F-54506 Vandoeuvre-lès-Nancy Cedex, France, thierry.bastogne@univ-lorraine.fr
2INRIA BIGS, BP 70239, F-54506 Vandoeuvre-lès-Nancy Cedex, France
3CYBERnano, 9 av. de la forêt de Haye, Campus Médecine, BP 184, F-54505 Vandoeuvre-lès-Nancy
4CEA, LETI-MINATEC, Département des Technologies pour la Biologie et la Santé, 17 rue des Martyrs, F-38054 Grenoble, France
5CEA, DSV iRTS, Biologie à Grande Échelle, Biomics, 17 rue des Martyrs, F-38054 Grenoble, France
6INSERM, U1038, F-38054 Grenoble, France
7Université Joseph Fourier-Grenoble I, U1038, F-38041, France

Abstract.

In this study, an empirical modelling-based method is proposed and implemented to identify the critical quality attributes and speed up the formulation optimization of a nanostructured lipid carrier.

Design of experiments. A mixture design with five factors, each associated with the nanoparticle formulation, was used: cationic lipid concentration (X1), fusogenic lipid concentration (X2), PEG surfactant concentration (X3), lecithin concentration (X4) and the hydrodynamic diameter (X5). The first four factors are dependent on each other and obey to a constraint equation about the nanoparticle composition. The nanoparticle properties considered were polydispersity (Y1), stability (Y2) and transfection efficiencies on the Hela (Y3) and PC3 cell lines (Y4).

Rational methodology of nanoparticle design. The empirical modelling methodology was split up into three consecutive steps. In the first part, we show that only the hydrodynamic diameter of the nanoparticle has a significant influence on the polydispersity response and we deduce its design space. In the second step, an empirical model of the nanoparticle stability is obtained, which allows us to identify two main contributors: the nanoparticle size and the concentration of surfactant PEG. A stability region in the (X3, X5) space is derived from this model. In the final part of this study, two response surface models are computed from the experimental data and are used to determine the optimal values of three formulation factors of the nanostructured lipid carrier.

Results. Two different formulations have been synthetized and their in vitro properties have corroborated the predicted values provided by the previous models. This study confirms that a rational and rigorous engineering of nanoparticles is possible, owing to statistical design of experiments and empirical modelling techniques. Such approaches can drastically reduce the preclinical development duration of nanotechnologies in medical applications.
Nanostructured lipid carrier 5 formulation factors

Statistical experimental design for formulation

Rational selection of the size

Optimized formulation

Optimization of the siRNA transfection (cell line 2)

Optimization of the siRNA transfection (cell line 1)

Determination of the stability region

Fig. 1 Empirical Model-based methodology to speed up the formulation optimization process of engineered nanoparticles.