



HAL
open science

Empirical model-based identification of critical quality attributes in the preclinical design of nanostructured lipid carriers

Thierry Bastogne, Jonathan Bruniaux, François de Crécy, Fabrice Navarro

► To cite this version:

Thierry Bastogne, Jonathan Bruniaux, François de Crécy, Fabrice Navarro. Empirical model-based identification of critical quality attributes in the preclinical design of nanostructured lipid carriers. 7th European Summit for Clinical Nanomedicine and Targeted Medicine, CLINAM 7, European Foundation for Clinical Nanomedicine, Jun 2014, Basel, Switzerland. hal-01078944

HAL Id: hal-01078944

<https://hal.science/hal-01078944v1>

Submitted on 30 Oct 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Empirical Model-based Identification of Critical Quality Attributes in the Preclinical Design of Nanostructured Lipid Carriers.

T. Bastogne^{1,2,3}, J. Bruniaux^{4,5,6,7}, 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 iRTSV, Biologie à Grande Echelle, Biomics, 17 rue des Martyrs, F-38054 Grenoble, France 3 INSERM, U1038, F-38054 Grenoble, France

⁶INSERM, U1038, F-38054 Grenoble, France

⁷Université Joseph Fourier-Grenoble I, U1038, F-38041, France

Abstract.

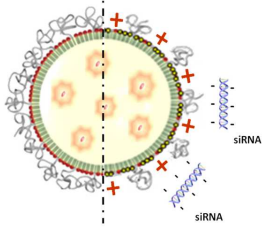
In this study, an empirical modelling-based method is proposed and implemented to identify the critical quality attributes and speed up the formulation optimization of a nanostructured lipid carrier.

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 dependant of each other and obey to a constraint equation about the nanoparticle composition. The nanoparticle properties considered were polydispersity (Y1), stability (Y2) and transfection efficacies on the Hela (Y3) and PC3 cell lines (Y4).

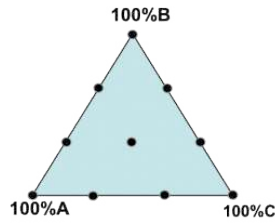
Rational methodology of nanoparticle design. The empirical modelling methodology was split up into three consecutive steps. In the first part, we show that only the hydrodynamic diameter of the nanoparticle has a significant influence on the polydispersity response and we deduce its design space. In 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 synthesized 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.

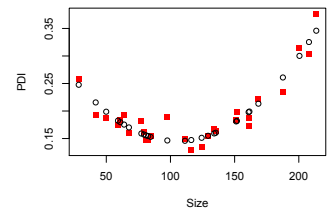
Nanostructured lipid carrier
5 formulation factors



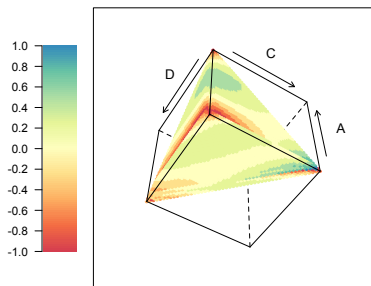
Statistical experimental
design for formulation



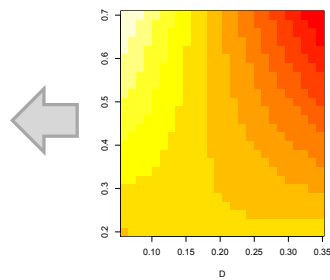
Rational selection
of the size



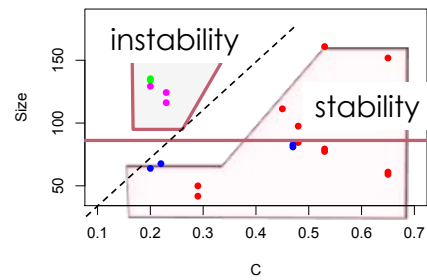
Optimized
formulation



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.