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

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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 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.

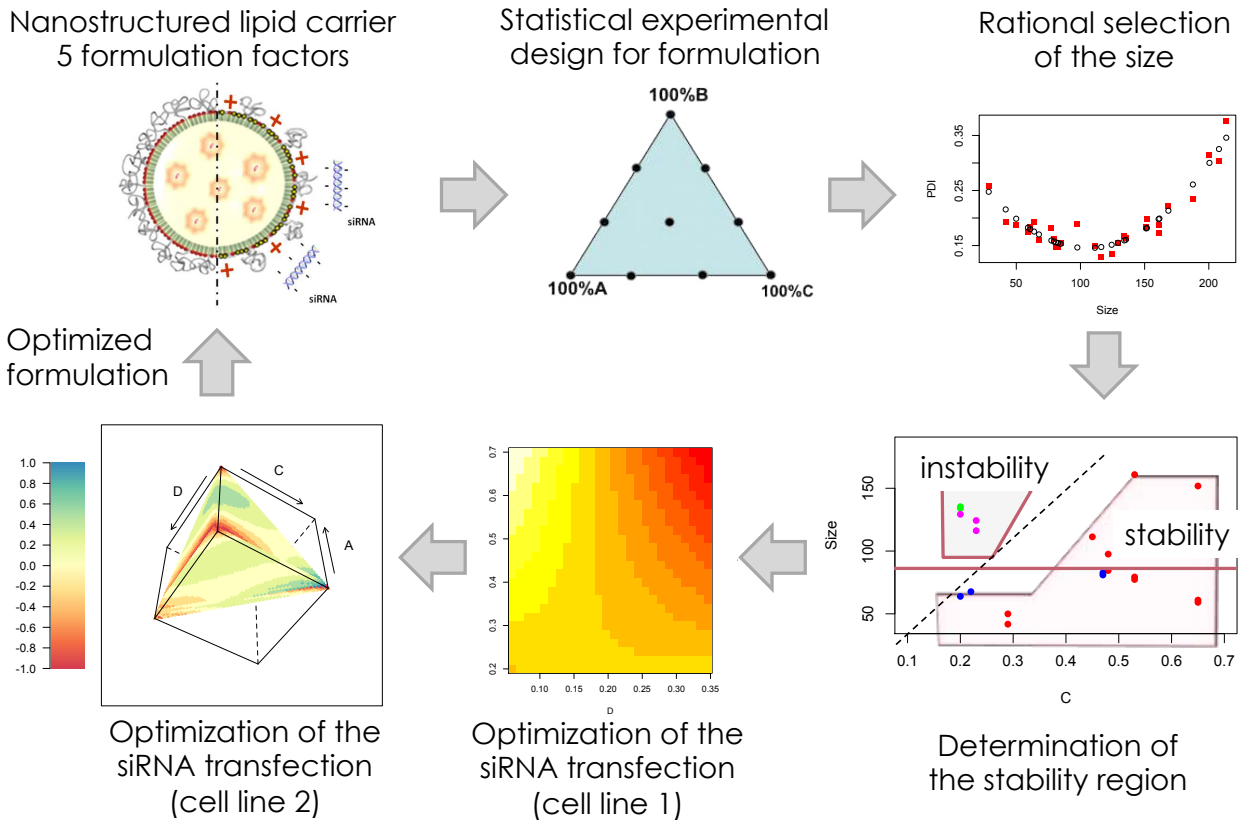

Fig.1 Empirical Model-based methodology to speed up the formulation optimization process of engineered nanoparticles.