


## Chapter 6

# Optimizing the Size of Drug-Loaded Nanoparticles Using Design of Experiments: Solid Lipid Nanoparticles

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### ABSTRACT

*Nanoparticles formed from lipids are currently applied successfully to deliver drugs. The particle size of the nanoparticle system is an essential characteristic to enhance the entrance of the drugs inside tissues and cells. Using design of experiment is appealing to find the specific conditions to optimize particle size of drug-loaded nanoparticles. Authors of this chapter applied a fractional factorial design of half fraction  $2^{4-1}$  with levels between continue factors, finding statistically significant differences for two factors such as concentrations of drugs and type of solvent where the organic phase is dissolved. This design shows the optimization of a formulation of capsaicin in solid lipid nanoparticles. The chapter also includes information on methods to prepare solid lipid nanoparticles (SLN), the variables involved, and a selection of studies about optimization of SLN formulations.*

DOI: 10.4018/978-1-7998-1518-1.ch006

## **INTRODUCTION**

Nanoparticles made with biocompatible materials have become very popular as drug delivery systems due to the ability to control drug release and to the possibility of their administration by parenteral routes. Modification of nanoparticle surface with ligands can provide site-specific drug delivery for the treatment of tumors or inflamed tissue (Siafaka, Üstündağ Okur, Karavas, & Bikiaris, 2016; Wissing, Kayser, & Müller, 2004).

Passive vectorization is possible taking advantage of the enhanced permeation retention effect consisting in an increased permeability into tumors and inflamed tissue driven by bigger fenestration than healthy tissue, and the lack of lymphatic drainage, which retains the nanoparticles in the tumors where loaded antineoplastic drugs can be delivered (Nakamura, Mochida, Choyke, & Kobayashi, 2016).

Solid lipid nanoparticles (SLN) are a type of nanomaterial that has shown to increase the bioavailability of orally administered drugs with poor water solubility and enhancer of drug concentration on dermal delivery, since the nanometric scale increases dissolution velocity and saturation solubility, resulting in improved absorption of loaded drugs. Routes of administration for SLN have been extended to dermal, transdermal, ocular, pulmonary and rectal (Din et al., 2015; Hu, Jia, & Ding, 2010; Sharif Makhmal Zadeh, Niro, Rahim, & Esfahani, 2018; Sharma, Jindal, Aggarwal, & Jain, 2010).

The chapter presents general information about the preparation and application of SLN, and a summary of researches that applied Design of Experiments (DoE) to optimize the size and another parameters of drug-loaded SLN. In most studies, lipid and surfactant used for the preparation of SLN stand out as independent factors, evaluating the influence over particle size and entrapment efficient (EE), principally (Table 1). The chapter provides information about the principal methods to produce SLN. Subsequently, a formulation of capsaicin-loaded SLN is describe as a case of study applying DoE. The purpose is to optimize the particle size of the drug-loaded SLN using a fractional factorial design  $2^{(k-p)}$ . The design has two levels and IV resolution to estimate main effects, plus two central points per block and two blocked replicates ( $n=3$ ); selecting as experimental factors: drug contained, lipid content, stabilizer content, and type of solvent. This design was selected to study the effect of the experimental factors on the response on particle size, combinate with the optimization of the process. In order to determine the best concentrations of capsaicin (CAP), Gelucire® 44/14 (lipid) and polyvinyl alcohol (PVAL) (surfactant) to generate the smaller particle size to be used in topical formulations, since particle's size less than 500 nm is crucial to transdermal delivery (Al-Kassas et al., 2016). The SLN were synthesized by an adaptation of the solvent emulsion-diffusion method, for the suitability to make small particles at room temperature (RT), in a few steps, using just one solid lipid, and stabilized with PVAL.

## **BACKGROUND**

Lipid-based carriers are particularly suited for topical application (Mahant, Rao, & Nanda, 2018). Liposomes are spherical vesicles composed of one or more phospholipid bilayers, representing the first generation of the novel lipid colloidal carriers after submicron emulsion-bases products were developed in 1960s (Joshi & Müller, 2009; Mehnert & Mäder, 2012). Liposomes offered encapsulation of hydrophobic and hydrophilic drugs but have many disadvantages, including short shelf life, poor stability, low encapsulation efficacy, and cell interactions (Czajkowska-Kośnik, Szekalska, & Winnicka, 2019).

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