PHARMACEUTICAL NANOTECHNOLOGY

Experimental Design for the Optimization of Lipid Nanoparticles

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ABSTRACT: Solid lipid nanoparticles (SLN) have been extensively investigated as a promising drug delivery system for controlling the release of therapeutic agents. Currently, there are many manufacturing methods available for SLN, including the high pressure homogenization method and the microemulsion technique. In addition, the solvent diffusion method has been discussed as an alternative technique in the literature, and has attracted great interest due to its simplicity and ease of handling. In order to gain a deeper understanding of this method, a statistical central composite design was applied in this study to examine how the physicochemical properties of the SLN were influenced by the variation of process parameters, including injected solvent, lipid concentration, surfactant concentration, temperature, and stirring speed. Our study showed that lipid concentration and temperature seemed to be the crucial parameters for the particle size of the monostearin SLN prepared by the solvent diffusion method. However, neither of these factors had a significant quadratic relationship with the zeta potential.
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Keywords: experimental design; solid lipid nanoparticles; solvent diffusion; particle size; zeta potential

INTRODUCTION

Solid lipid nanoparticles (SLN) have been used as a drug delivery system for controlling the release of various drugs.[1] Several preparation techniques for SLN have been developed in the last decade, including high-pressure homogenization,[2] microemulsion techniques,[3] and solvent emulsification/evaporation methods.[4] The solvent diffusion method is another novel technique that has been reported in the literature recently for the preparation of SLN.[5,6] This technique is commonly employed for the preparation of liposomes and polymer nanoparticles, and offers clear advantages over existing methods such as ease of handling and a fast production process, without the need for technically sophisticated equipment.[7]

To prepare SLN by the solvent diffusion method, the drug and lipid are dissolved in organic, water-miscible solvents at elevated temperatures and the resultant solutions are rapidly injected into an aqueous phase containing surfactants, under mechanical stirring.[5,6] As the

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temperature cools, the lipid droplets solidify and thus SLN suspensions of the active drugs form. During the manufacturing process, many parameters appear to have a marked influence on the physicochemical properties of SLN. It is, therefore, essential to have a clear understanding of how preparation conditions determine particle characteristics and, in particular, how these characteristics are influenced by potential interactions between variables in the preparation process. Although the effects of preparation variables on the physicochemical properties have been reported,[7] a systematic investigation of the simultaneous influence of multiple formulation variables on the SLN properties has not yet been undertaken.

Evaluating the effect of a large number of formulation variables usually requires many experiments, which are often costly and time consuming. It is therefore prudent to minimize the total number of experiments performed in the optimization process, without sacrificing final product quality. Central composite design (CCD) has been used widely to find the operating parameters that optimize a specific manufacturing process.[8] CCD is a collection of mathematical and statistical techniques that are useful for the modeling and analysis of problems composed of matrices of variables.[9,10] Essentially, a relatively small number of empirical evaluations are used to determine mathematical trends that allow the prediction of final process parameters needed for a specific, optimized outcome. The CCD evaluation efficiently provides information on how the response of interest is influenced by several variables. This statistical tool significantly reduces the number of empirical experiments that are necessary to identify a mathematical trend in the experimental design, facilitating determination of the optimum level of variable factors required for a given response or result.[11] The application of CCD is very flexible in design, allowing process evaluation under different experimental conditions of interest and operability.

Therefore, the aims of the study were to evaluate the potential of a high throughput statistical screening method for theoretically optimizing the unit process parameters influential in the preparation of SLN, and to investigate the practical success of the predictive statistical process in the production of optimized SLN vehicles without the need for extensive empirical evaluation of the complex myriad of process parameters.

MATERIALS AND METHODS

Materials

Lecithin, poloxamer 188, tween 80, Sodium Dodecyl Sulfate, benzalkonium chloride, acetone, ethanol, and isopropanol were purchased from Fisher Scientific (Fairlawn, NJ). Monostearin (glyceryl monostearate) was purchased from Spectrum Chemical Mfg. Corp. (New Brunswick, NJ). Double-distilled, deionized water for HPLC was used throughout this study.

Methods

Preparation of SLN

The monostearin was completely dissolved in 5 mL of a water-miscible solvent in a water bath at 70°C. Three solvents were used for screening purposes: Ethanol, isopropanol, and acetone. The resultant organic solution was injected into 50 mL of an aqueous phase containing surfactant at different temperatures, under mechanical agitation for 30 min. The nanosuspensions or nanoemulsions formed were then cooled to room temperature, resulting in SLN formations. The specific amount of ingredients added during the preparation strictly followed the experimental design conditions in Table 1.

Characterization of Physicochemical Properties

The particle size, polydispersity index, and electrophoretic mobility (zeta potential) of manufactured SLN dispersions were measured by Zetapals (Zetapals, Brookhaven Instruments, Holtsville, NY). Each sample was diluted with filtered, double-distilled water until an appropriate concentration of particles was achieved to avoid multiscattering events when measuring for 10 min in serial mode, with a sample time of 30 ms. The electrophoretic mobility was converted to a

Table 1. Factor Level Applied in the Optimization

	Factor Level in Design				
Factor	−2	−1	0	+1	+2
X_1 lipid (mg/mL)	1	7	13	19	25
X_2 surfactant (%)	0	0.5	1	1.5	2.0
X_3 stirring speed (rpm)	100	300	500	700	900
X_4 temperature (°C)	20	35	50	65	80

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