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A multivariate modeling for analysis of factors controlling the particle size and viscosity in palm kernel oil esters-based nanoemulsions

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ABSTRACT

An artificial neural network (ANN) was used to develop predictive models for studying and identifying factors that influence particle size and viscosity of sodium diclofenac-loaded palm kernel oil esters-nanomeulsions. The effect of four independent variables namely water content, oil and surfactant (O/S) ratio, mixing rate and mixing time were considered as inputs of the network trained. The particle size and viscosity of samples in various compositions prepared under different rate and time of high shear emulsification, were measured as output. Data, split into training, testing and validating sets, were modeled by incremental back propagation (IBP) algorithm. The developed model represents high quality performance of the neural network and its capability in modeling and identifying the critical factors that control preparation of the nanoemulsions. Water content with 30.82% importance was found to be the main parameter controlling the particle size and viscosity in the system, followed by O/S ratio, mixing rate and mixing time, with 27.28, 22.06 and 19.84% importance, respectively. The model was then employed to investigate the effect of composition and processing factors on particle size and viscosity of the nanoemulsions.

1. Introduction

Nanoemulsions are nano-size scale emulsions with droplet size ranging from 20 nm to 500 nm. Due to its small particle size and very good stability, nanoemulsions has unique properties to be used in many practical applications such as personal care and cosmetics (Teo et al., 2010), agrochemical (Lim et al., 2012), food (Silva et al., 2012), chemical (Ragupathy et al., 2011) and pharmaceuticals (Machado et al., 2012).

An emulsion is formed by dispersion of one liquid, usually oil phase in another immiscible liquid, water phase. In comparison to other oils, palm kernel oil esters (PKOEs) contain higher amount of shorter chain esters and can be applied as a carrier for actives. Palm kernel oil esters are known for their excellent wetting behavior without the oily feeling. Furthermore, the higher iodine and saponification values as well as lower slip melting point of palm kernel oil esters in comparison with other esters, provide some favorable properties for micro and nanoemulsions to be used in many applications such as cosmetics (Keng et al., 2009) and pharmaceutics (Salim et al., 2012). For nanoemulsion nonequilibrium systems, extrinsic energy is necessary. There are two main methods for the preparation of nanoemulsions: condensation or low-energy methods, and dispersion or high-energy methods. High-energy emulsification methods result in emulsions having the most homogeneous flow and adjustable control of droplet size and thus are suitable for industrial utilizations (Solans et al., 2005). However, despite the formation mechanism, the prepared nanoemulsions properties are influenced by formulation compositions (Tcholakova et al., 2004; Yuan et al., 2010).

In this work, the formation of nanoemulsions in the PKOEs/Lecithin:Cremophor EL/water system was performed by high-shear stirring method for transdermal drug delivery of sodium diclofenac. In order to overcome the drug adverse effects, high hepatic first-pass metabolism and the short biological half-life, the development of a transdermal nanodelivery system like nanoemulsions is beneficial. For transdermal delivery of nanoemulsions containing drug, minimization of particle size as well as reduction in viscosity exhibit faster release of active ingredients and enhance drug permeation (Cross et al., 2001; Fang et al., 2003; Tsai et al., 2011). Although, it has been found that the viscosity is an important parameter for stability and an efficient drug release, there are

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few reports on the effect of factors on nanoemulsions viscosity or its optimization, especially in pharmaceutical research. There are a number of literatures which studied the dominating factors that determine the particle size of nanoemulsions. These studies were performed by considering the concentration of internal phase of the emulsion (Moreno et al., 2003; Malcomson et al., 2002), concentration of surfactant, co-surfactant or other compositions (Moreno et al., 2003; Amani et al., 2008; Park and Kim, 1999). However, less has been done on optimizing the processing parameters. On the other hand, it is advantageous to achieve a model to study and optimize the processing conditions such as time and rate in high-energy method in order to avoid extra time and energy consumption, particularly in industrial application. The preparation and formulation of nanoemulsions with some desirable properties are difficult to model by classical statistical techniques due to the non-linear relationships between components and/or processing conditions. Furthermore, a desirable formulation for one characteristic is not always desirable for other properties (Amani et al., 2008).

In recent years, artificial neural network (ANN) has been introduced in pharmaceutical applications as a powerful tool for dealing with complex multivariate non-linear relationships (Amani et al., 2008; Sathe and Venitz, 2003). ANN is an artificial neuron to simulate the way in which biological neurons process information. It contains an interconnected group of neurons to process the modeling for prediction of the behavior of a given system, design new processes and analyze existing processes (Ebrahimpour et al., 2008; Cavas et al., 2011). Furthermore, these processes can be performed in a short computing time with high potential for sufficient quality adaptive performance (Adnani et al., 2011). ANN has been successfully applied in analysis and modeling in pharmaceutical research such as designing of controlled release drug delivery systems (Sun et al., 2003), improving understanding of the process of formation of nanoemulsions (Agatonovic-Kustrin and Alany, 2001) and stability evaluation of nanoemulsions (Amani et al., 2010).

The objective of the present study was to study and identify the critical factors in the preparation mechanism such as mixing rate and mixing time as well as O/S ratio and water concentration, which control the particle size and viscosity in the PKOEs-based nanoemulsions.

2. Materials and methods

2.1. Materials

Palm kernel oil esters (PKOEs) were prepared in our laboratory. Soyabean lecithin (lipoid S75) was purchased from Lipoid GmbH (Ludwigshafen, Germany) and used without further purification. Cremophor EL and sodium diclofenac were obtained from Sigma–Aldrich (St. Louis, MO, USA) and Santa Cruz Biotechnology (Dallas, USA), respectively. Water used was doubled distilled water (Milli-Q deionized water, Millipore, Billerica, MA, USA).

2.2. Construction of phase diagram

Pseudo-ternary phase diagram was constructed using different proportions of the palm kernel oil esters to the mixture of Lecithin (L):Cremophor EL (Cr EL) with a ratio of 60:40. An appropriate weight of water was added to the samples. The mixtures were vortexed for 10 min with vortex mixer Model VTX-3000L (Japan) and then centrifuged using Hermle Model Ettek (Germany) at 4000 rpm for 15 min. The phase changes of the samples were determined visually through cross-polarized light. The above steps were carried out at room temperature. The phase diagram was constructed using software, Chemix version 3.5 phase diagram plotter (UK).

2.3. Nanoemulsions preparation

Oil-in-water (O/W) nanoemulsions selected from the isotropic phase were prepared by continuous addition of aqueous phase at 25 ± 2 °C to the surfactants-oil mixture. The final concentration of sodium diclofenac in the nanoemulsions was 1.0 wt% dissolved in water as aqueous phase. Lecithin and cremophor EL were used as surfactant in the system. Lecithin was dissolved in the oil phase (palm kernel oil esters). Cremophor EL was added to the mixture and homogenized under simple stirring. The aqueous phase was then added dropwise to the oil phase to attain equilibrium state. The resultant emulsions were then homogenized by a high shear stirrer (IKA® RW 20 Digital, Nara, Japan). After the homogenization, the nanoemulsions were collected and kept overnight to equilibrate. Then, their particle size and viscosity were analyzed.

2.4. Particle size measurements

SympaTec GmbH Nanophox particle size analyzer (Clausthal-Zellerfeld, Germany) with Photon Cross Correlation Spectrometer (PCCS) was used to determine the mean droplet size of the nanoemulsions at 25 °C. After dilution, the samples were loaded into 1 cm^2 cuvettes in a thermostated chamber. The scattering intensity measurements were achieved at an angle of 90°.

2.5. Viscosity measurement

Viscosity measurements were performed using Kinexus Rotational Rheometer (Malvern Instruments Ltd.). The measurements were carried out at the temperature of 25.0 °C ± 0.5 °C at 5 s^{-1} shear rate. Data points were the average of two measurements on each sample.

2.6. Experimental design

A 5-level-4-factor central composite rotatable design (CCRD) was employed using the Design-Expert version 6.0.6 (State-Ease Inc., Statistics Made Easy, Minneapolis, MN, USA). Four parameters consisting of compositions and processing factors as input variables were considered for the preparation of 30 nanoemulsion formulations: water content (%, w/w), oil and surfactant (O/S) ratio, mixing rate (rpm) and mixing time (min). Data generated through CCRD was divided into three subsets: training point (20 data point), test set (4 data points) and validation set (6 data points). The splitting of data into training, validation and test subsets was performed to estimate the quality of the network during training and to evaluate the performance of the network for prediction of "unseen" data that were not used for training. Table 1 shows the values of inputs used for training, testing and validating the network.

2.7. ANNs model

2.7.1. Software tool

The commercial ANN software NeuralPower version 2.5 (CPC-X Software) was employed in the ANN studies. A multilayer feedforward neural network containing three layers was used to model relationships in complex nonlinear between inputs and outputs and resulted as 3D graphs instead of statistical models because of its powerful nonlinear mapping capability.

2.7.2. Neural network architecture

Nanoemulsions preparation is not a process that depends on any parameter alone instead a combination of parameters affects the properties. Artificial neural network presents a powerful tool