Development and Optimization of Self-Nanoemulsifying Drug Delivery System with Enhanced Bioavailability by Box–Behnken Design and Desirability Function

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ABSTRACT: The aim of our study was to characterize and optimize a self-nanoemulsifying drug delivery system (SNEDDS) formulation by a three-factor, three-level Box–Behnken design (BBD) combined with a desirability function. The independent factors were the amounts of Capryol PGMC (X_1), Tween 20 (X_2), and Transcutol HP (X_3). The dependent variables were droplet size (Y_1), equilibrium solubility (Y_2), and cumulative percentage of drug released in 15 min (Y_3) from the SNEDDS formulation. The responses were fitted to a second-order quadratic model and statistical validation of the fitted models was carried out by analysis of variance. Various response surface graphs and contour plots were constructed to understand the effects of different factor level combinations on the responses. The optimized SNEDDS formulation consisting of Capryol PGMC–Tween 20–Transcutol HP at proportions of 5:58.4:40 (w/w) was prepared and a comparison of the predicted values and experimental values was found to be in close agreement. Furthermore, an *in vivo* pharmacokinetic study of the optimized SNEDDS formulation showed a 2.2-fold increase in relative oral bioavailability compared with that of the suspension. In conclusion, the BBD demonstrated its effectiveness in optimizing the SNEDDS formulation and in understanding the effects of formulation variables on the performance of SNEDDS. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:4584–4596, 2012

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INTRODUCTION

More than 68% of oral drugs in the early developmental stage possess poor aqueous solubility (<100 μg/mL),[1] resulting in insufficient dissolution in the gastrointestinal (GI) tract following oral administration, which ultimately leads to poor bioavailability and suboptimal efficacy.[2] Therefore, in recent years, much interest has been focused on improving the solubility of poorly water-soluble drugs either by using formulation strategies such as crystal engineering,[3] solid dispersion,[4] cyclodextrin complexation,[5] lipidic systems,[6,7] micronization, and nanosization,[8,9] or chemical strategies such as salt formation[10] and prodrugs.[11,12]

Among the formulation strategies is the self-nanoemulsifying drug delivery system (SNEDDS), a lipid-based nonparticulate drug delivery system that enhances the solubilization of highly lipophilic drugs. The SNEDDS is isotropic mixtures of oil(s), surfactant(s), and cosurfactant(s) that, upon dilution in GI fluid, followed by mild peristaltic agitation, can rapidly form oil-in-water (o/w)-type nanoemulsions of droplet sizes ranging from 20 to 200 nm.[13] The SNEDDS is typically developed by following an empirical, trial-and-error approach that, besides being highly time consuming and cost ineffective, does not

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guarantee a true "optimum" formulation composition. This traditional approach of blending excipients (factors or variables) in different ratios and evaluating the key performances of each composition can achieve satisfactory results, but better formulations might exist for studied formulation variables.

Recently, the response surface methodology (RSM), using proper experimental designs, has become widely used for formulation optimization. The Box–Behnken design (BBD) is one of the RSMs that could be a suitable approach for understanding the effects of formulation variables (independent factors) and the interactions between factors on the responses (dependent factors). The BBD usually takes factors at three levels and all the design points fall within the safe operating zone. In each run, the levels of two factors are held at their extreme levels and the third at its middle level, thereby reducing the experimental runs performed with the highest or lowest levels. However, because the level of one factor in each run is always in the mid-level, BBD may introduce errors if extrapolated to extremes of the design space and is appropriate only when it is certain that the factor and response do not follow linear model. Despite its poor coverage of the corner of nonlinear design space, BBD is still considered to be more efficient and most powerful than other designs such as the central composite design (CCD), Doehlert design, and three-level full factorial design.[14] Moreover, it requires fewer experimental runs than CCD and three-level full factorial design, and is consequently less expensive. It has been successfully used to optimize the preparation of sustained-release pellets[15] and oral controlled-release delivery systems[16] and to gain an understanding of the formulation variables of SNEDDS.[17,18]

The aim of our study was to develop an optimized formulation by employing the BBD in combination with a desirability function and to evaluate the main effects, interaction effects, and quadratic effects of SNEDDS formulation variables on three responses: the droplet size, equilibrium solubility, and the cumulative percentage of drug released in 15 min. For this purpose, flurbiprofen, a Biopharmaceutical Classification System class II drug,[2] was used as the model drug.

MATERIALS AND METHODS

Materials

Flurbiprofen was supplied from Kolon Life Science Company (Kwacheon, Korea). Polyglycolyzed glycerides (Capryol PGMC, Cremophor EL, Labrafac CC, Labrafil WL 2609, Labrafil M 1944 CS, Labrafil M 2125 CS, and Transcutol HP) were obtained from Gattefosse (Saint-Priest Cedex, France). Castor oil, corn oil, cotton seed oil, mineral oil, sesame oil, sunflower oil, and peanut oil were supplied by Sigma–Aldrich Company (St. Louis, Missouri). Polysorbate 20 (Tween 20), sorbitan monolaurate 20 (Span 20), sorbitan monooleate 80 (Span 80), and labrasol were purchased from DC Chemical Company (Seoul, South Korea). All other chemicals were of analytical grade and were used without further purification.

Methods

Solubility Studies

An excess amount of flurbiprofen powder was added to 2 mL microtubes (Axygen MCT-200) containing 1 mL of the selected vehicles (oils or surfactants). The mixtures were vortexed and shaken in a water bath for 84 h at 25°C and 100 rpm, followed by centrifugation at 3000 *g* for 15 min (Eppendorf, Haupauge, New York). The supernatant was filtered through a polyvinylidene fluoride (PVDF) Syringe filter (0.45 μm) and diluted with acetonitrile to quantify the flurbiprofen using a high-performance liquid chromatography (HPLC) system. The HPLC (Hitachi, Japan) consisted of Hitachi model D-2000 elite chromatography data station software version 2.0, a Hitachi L-2130 pump, and a Hitachi L-2400 UV–VIS detector. The column used was an Inertsil ODS-3 reverse-phase C18 column (0.5 μm, 25 × 0.46 cm^2, internal diameter; GL science, Torrance, California). The mobile phase, a mixture of water, acetonitrile, and phosphoric acid (400:600:5, v/v), was eluted at a flow rate of 1.5 mL/min. The effluent wavelength was monitored at 254 nm.

Construction of the Ternary Phase Diagram

A ternary phase diagram of the oil, surfactant, and cosurfactant was constructed to identify the area of the self-emulsification system. A visual test method reported by Craig et al.[19] was modified and used in the study. A series of blank SNEDDS formulations consisting of the oil phase, Capryol PGMC; surfactant, Tween 20; and the cosurfactant, Transcutol HP, were prepared at different ratios. Then, 0.2 mL of each formulation was introduced into 200 mL of water in a glass beaker at 37°C and gently stirred with a magnetic bar. The tendency to form a nanoemulsion was visually judged to be qualitatively good when the droplets spread easily in water, forming a fine transparent or slight bluish dispersion, and it was considered bad when there was a milky, poor, or no emulsion formation due to the immediate coalescence of the oil droplets, especially when stirring was stopped. Ternary phase diagrams are used to determine the efficient self-emulsifying region, that is, the feasibility of nanoemulsion formation at extreme values of the excipients. Therefore, the extreme and middle levels of the independent variables, consisting of the oil,