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# Design and optimization of a new self-nanoemulsifying drug delivery system

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ABSTRACT

To improve the dissolution rate of ibuprofen, a model poorly water soluble drug, self-nanoemulsifying drug delivery systems (SNEDDS) were developed. Various surfactants and oils were screened as candidates for SNEDDS on the basis of droplet size of the resulting emulsions. The influence of the constituent structure, concentration and the composition of SNEDDS formulations, and the emulsifier HLB value, on the properties of the resulting emulsions was systematically investigated. Several SNEDDS formulations were employed to study the relationship between the emulsion droplet size and the dissolution rate of ibuprofen. The dissolution rate was accelerated by decreasing the nanoemulsion droplet size, and was significantly faster than that from a conventional tablet. The optimal SNEDDS formulation had a mean nanoemulsion droplet diameters of 58 nm in phosphate buffer, pH 6.8 (simulated intestinal fluid), and released ibuprofen more than 95% within 30 min. Therefore, these novel SNEDDS carriers appear to be useful for controlling the release rate of poorly water soluble drugs.



## 1. Introduction

Due to the convenience and improved patient safety, oral administration is the preferred method of drug administration. For any orally-administered drug, the pharmacological effect relies on involved mechanism of transport from the site of entry into the body to the site of action [1]. The oral delivery of poorly water soluble drugs presents a major challenge because of the low aqueous solubility of such compounds. For such compounds, the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution [2]. Much attention has been used to increase the drug solubility and dissolution properties, such as the use of surfactants, water-soluble carriers, polymeric conjugates and solid dispersions [3,4]. In recent years, the most popular approach is the incorporation of the active poorly water soluble component into inert lipid vehicles such as surfactant dispersions [5], microemulsions [6], nanoemulsions [7], self-emulsifying formulations [8], self-microemulsifying formulations [9], emulsions [10,11] and liposomes [12].

Droplet size of the carrier is of key importance for the dissolution rate of low water solubility drugs. It has been reported that the particle size distribution is one of the most important characteristics of the in vivo fate of cyclosporine emulsion [13]. Nicolaos et al. [14] also reported the bioavailability of cefpodoxime proxetil increased from 50 to 98 wt% when using submicronic emulsions for oral administration. Recent investigations show that the dissolution rate of griseofulvin particles with sizes in the range of 200 nm is about two-fold higher than for the conventional micronized material [15]. However, submicron emulsions and particles are very difficult to be produced in solid dosage forms, and particle size reduction may result in handling difficulties and poor wettability. To overcome these drawbacks, a self-nanoemulsifying drug delivery system (SNEDDS) would be an efficient, convenient, flexible and more patient-friendly approach.

SNEDDS are isotropic mixtures of oil, surfactants and co-surfactants that form fine oil-in-water nanoemulsions upon mild agitation, followed by injection into aqueous media, such as GI fluids [16]. SNEDDS can be orally administered in soft or hard gelatin capsules due to the anhydrous nature, typically producing nanoemulsions with droplet sizes between 20 and 200 nm upon dilution. When compared with emulsions, which are sensitive and metastable dispersed forms, SNEDDS are physically stable formulations that are easier to manufacture, and may offer an improvement in dissolution rates and extents of absorption, resulting in more reproducible blood–time profiles due to the nanometer sized droplets present. Although droplet size was widely proposed as being a key factor for the efficiency and of SNEDDS applications [7,16–18], the factors influencing the droplet sizes formed in SNEDDS have not yet been studied systematically. The lack of knowledge is addressed by this work which is a systematic study of the effect of emulsifier hydrophile–lipophile balance (HLB), as well as the structure of emulsifiers and oils on the final nanoemulsion droplet size. The results show how it is possible to control the

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preferred droplet sizes in nanoemulsions generated from model SNEDDS.

The poorly water soluble ibuprofen, which is a nonsteroidal anti-inflammatory drug (NSAID), has been used for decades in the management of a multitude of pain conditions and rheumatic diseases. Because of a longstanding and favorable safety record, as well as proven efficacy in many different populations and indications, the popularity of ibuprofen is ever increasing [19]. Ibuprofen is highly permeable through physiological membranes and its bioavailability is close to 100% because of almost complete absorption, however, the onset of absorption strongly depends on dissolution. Ibuprofen shows low solubility in aqueous acidic media, and thus its dissolution depends on the administered formulation. The vast majority of pain treatment therapies require a fast onset of action, therefore, different approaches have been made to improve ibuprofen dissolution, such as transferring the substance to a salt (lysinate) or designing a pharmaceutical dosage form that favors a quick release of ibuprofen in the GI tract [1]. In this work, ibuprofen is incorporated into the SNEDDS to improve its dissolution rate.

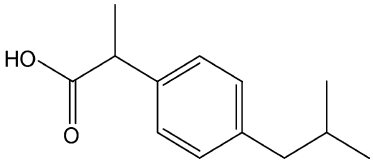
Experimentally, the following were conducted:

(a) The factors influencing droplet sizes of resulting emulsion diluted from SNEDDS were screened, and optimal SNEDDS for drug loading were obtained.
(b) Ibuprofen was loaded as a model water poorly drug onto the SNEDDS. Its influence on the droplet size and stability of resulting nanoemulsion was characterized. The relationship between the ibuprofen dissolution rate from SNEDDS and droplet size of resulting emulsion was investigated.

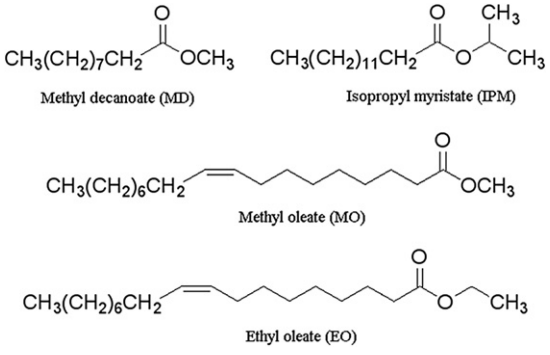
## 2. Materials and methods

### 2.1. Materials

Ibuprofen (Scheme 1) was a gift sample from Shandong Xinhua Pharmacy Co., Ltd. (China), and the conventional ibuprofen tablet (equivalent to 100 mg ibuprofen) is purchased from Beijing Taiyang Pharmacy Co., Ltd. (China). Methyl decanoate (MD), isopropyl myristate (IPM), methyl oleate (MO) and ethyl oleate (EO) are fatty acid esters with similar structures (Scheme 2). IPM and EO (purchased from Sinopharm Chemical Reagent Co., Ltd., China) are widely used as solvents in pharmaceutical formulations, and MD and MO (supplied by Wujiang Tianhong Food Corporation, China) also have low toxicities and can be used as reagent in pharmacy [20]. Various surfactants, polyoxyethylene sorbitan fatty acid esters (Tweens) and sorbitan fatty acid esters (Spans) were all purchased from Sinopharm Chemical Reagent Co., Ltd. (China). The structures and properties of surfactants are shown in Scheme S1 and Table S1 (seen in Supporting material), respectively. 1,2-Octanediol was used as cosurfactant and purchased from Sinopharm Chemical Reagent Co., Ltd. (China). All the materials were used as received. Water was twice distilled.




**Scheme 1.** Structures of ibuprofen.




**Scheme 2.** Structures of oils.

### 2.2. Preparation of self-nanoemulsifying system and droplet size determination

Homogeneous mixtures of emulsifiers and oils at mass fraction of 1:1 were blended for all the samples unless stated otherwise. The concentrate was homogenized at 25 °C for 3 days before use. Triplicate samples of selected concentrate containing various surfactants and oil compositions were diluted 100-fold with water, pre-equilibrated at 25 °C, and gently mixed by a magnetic stirrer. The droplet size of resulting emulsion was determined by dynamic light scattering (DLS) at a scattering angle of 173° (Zetasizer Nano-ZS, Malvern, UK) at 25 °C, employing an argon laser ($\lambda = 633$ nm).

### 2.3. Solubility studies

The solubility of ibuprofen in water, oil, surfactants, cosurfactant and selected SNEDDS was determined. An excess of ibuprofen (approximately 1 g) was placed in 2 ml of the vehicle in screw-capped glass vials, and the mixture was heated at 60 °C in a water-bath to facilitate solubilisation using a vortex mixer. Mixtures were equilibrated at 25 °C for 3 days in a water bath and then centrifuged at 12,000 rpm (Sigma-3K18, Sigma) for 10 min to separate the undissolved drug. Aliquots of supernatant were diluted with methanol and quantified by HPLC by reversed phase high performance liquid chromatography (RP-HPLC) with a UV detector at $\lambda = 222$ nm. The RP-HPLC system consisted of a pump (P680A LPG), a VIS–UV detector (UVD 170U), a data station (Chromeleon, DIONEX, USA). The mobile phase consisted of methanol: water (0.9 wt% phosphate acid) (85:15). The retention time of ibuprofen was 6.9 min when the flow rate was kept at 1 ml/min and column oven temperature was maintained at 40 °C.

### 2.4. Evaluation of ibuprofen-loaded SNEDDS

Various amounts of ibuprofen were dissolved in the oil, and then mixed with emulsifiers and stirred to ensure uniformity. The formulated SNEDDS were equilibrated at 25 °C for 3 days, and examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies. The droplet size of the resulting emulsions generated from ibuprofen-loaded SNEDDS was determined by Zetasizer Nano-ZS (Malvern, UK).

### 2.5. In vitro dissolution profile

The dissolution test was carried out using Dissolution Apparatus II (ZRS-6, Tianjin Wireless Factory, China) according to Chinese Pharmacopoeia dissolution procedure. SNEDDS formulations with ibuprofen equivalent to 100 mg was filled into gelatin hard capsules and put into a copper sinker. The sinker was loaded with 900 ml dissolution media (pH 6.8 phosphate buffer so as to simulate intestinal fluid) at 37 °C with a rotating speed of 100 rpm. During the study, 1 ml aliquots were removed at predetermined time intervals from the dissolution medium and 1 ml of fresh phosphate buffer was replaced. The amount of ibuprofen released