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The design of naproxen solid lipid nanoparticles to target skin layers

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ABSTRACT

The aim of the current investigation was to produce naproxen solid lipid nanoparticles (Nap-SLNs) by the ultrasonication method to improve its skin permeation and also to investigate the influence of Hydrophilic-lipophilic balance (HLB) changes on nanoparticles properties. The properties of obtained SLNs loaded with naproxen were characterized by photon correlation spectroscopy (PCS), transmission electron microscopy (TEM) and differential scanning calorimetry (DSC). FT-IR was also used to investigate any interaction between naproxen and the excipients used at the molecular level during the preparation of the SLNs. The performance of the formulations was investigated in terms of skin permeation and also the retention of the drug by the skin. It was found that generally, with increasing the lipid concentration, the average particle size and polydispersity index (PDI) of SLNs increased from 94.257 ± 4.852 nm to 143.90 ± 2.685 nm and from 0.293 ± 0.037 to 0.525 ± 0.038 respectively. The results also showed that a reduction in the HLB resulted in an increase in the PDI, particle size, zeta potential and entrapment efficiency (EE%). DSC showed that the naproxen encapsulated in the SLNs was in its amorphous form. The peaks of prominent functional groups of naproxen were found in the FT-IR spectra of naproxen-SLN, which confirmed the entrapment of naproxen in the lipid matrix. FT-IR results also ruled out any chemical interaction between drug and the chemicals used in the preparation of SLNs. The amount of naproxen detected in the receptor chamber at all the sampling times for the reference formulation (naproxen solution containing all surfactants at pH 7.4) was higher than that of the Nap-SLN8 formulation. Nap-SLN8 showed an increase in the concentration of naproxen in the skin layer with less systemic absorption. This indicates that most of the drug in Nap-SLN8 remains in the skin which can reduce the side effect of systemic absorption of the drug and increases the concentration of the drug at the site of the action.

1. Introduction

The development of new drugs alone is not sufficient to ensure progress in drug therapy [1]. To overcome problems such as poor absorption, rapid metabolism and elimination, poor water solubility and high fluctuation of plasma levels, development of suitable drug delivery systems is a good strategy [2]. Naproxen is a non-steroidal anti-inflammatory drug (NSAID) which is used with increasing frequency in the treatment of rheumatic diseases and related painful conditions [3]. Naproxen protein binding in plasma is high and also varied [4] and like other NSAIDs causes gastritis and peptic ulceration after oral administration [5]. If these drugs are administered topically they should be able to provide high concentration of the drug locally if the poor permeability of the stratum corneum is overcome [6]. In order to avoid the irritation of the gastrointestinal tract and minimizing the systemic toxicity, application of polymer-based nanoparticles such as PLGA and eudragit RL100 with controlled drug release pattern could be useful in the treatment of inflammatory diseases [7,8]. One of the other promising methods to reduce the side effect of naproxen is the topical administration route. Transdermal drug delivery systems provide the most important route to achieve these goals [9]. The transdermal delivery system enable controlled or sustained release of the

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Table 1
Component and physicochemical properties of investigated NAP-loaded SLN (% w/w). The data are the mean and standard deviation of three determinations (n = 3). NAP: naproxen; GMS: glyceryl monostearate; PDI: polydispersity index; zeta potential; EE: entrapment efficiency.

Formulation	Naproxen (%)	GMS(%)	Span 80 (%)	Tween 80 (%)	Water(%)	HLB	Particle Size* (nm)	PDI**	Zeta Potential** (mv)	EE%***
Nap-SLN1	0.061	0.305	0.651	1.302	Qs 100	11.4	94.3 ± 4.9	0.293 ± 0.037	−7.55 ± 0.23	66.35 ± 1.10
Nap-SLN2	0.061	0.609	0.649	1.298	Qs 100	11.4	105.5 ± 5.2	0.404 ± 0.012	−7.15 ± 1.09	59.46 ± 0.50
Nap-SLN3	0.060	1.210	0.645	1.290	Qs 100	11.4	143.9 ± 2.7	0.525 ± 0.038	−7.10 ± 0.46	59.83 ± 1.15
Nap-SLN4	0.061	0.305	–	1.954	Qs 100	14.9	84.5 ± 2.0	0.273 ± 0.044	−4.96 ± 0.16	59.95 ± 0.74
Nap-SLN5	0.061	0.305	0.210	1.744	Qs 100	13.8	100.0 ± 9.7	0.270 ± 0.107	−3.92 ± 0.71	60.24 ± 0.32
Nap-SLN6	0.061	0.305	0.488	1.465	Qs 100	12.3	140.7 ± 18.3	0.241 ± 0.020	−5.06 ± 0.78	61.64 ± 0.37
Nap-SLN7	0.061	0.305	0.814	1.115	Qs 100	10.5	162.2 ± 24.2	0.351 ± 0.046	−7.05 ± 2.21	62.45 ± 0.13
Nap-SLN8	0.061	0.305	1.122	0.831	Qs 100	8.7	252.6 ± 43.1	0.394 ± 0.081	−10.57 ± 0.57	62.91 ± 1.79

ANOVA test followed by Tukey's test showed that the effect of HLB on particle size, PDI, zeta potential and EE% was significant ($p < 0.05$).

* In the particle size column all the particle sizes are significantly different from each other (Tukey's test).

** The effect of HLB on PDI and zeta potential is more dominant when the difference in the HLB value is more than 1.8 (for example there is no significant difference between Nap-SLN8 and Nap-SLN7, but this difference was significant when Nap-SLN8 was compared to Nap-SLN6).

*** Nap-SLN1 is significantly different from the other formulations. The difference between SLN3, SLN4, SLN5, SLN6 and SLN7 is not significant ($p > 0.05$). The difference between SLN4 with SLN8 and SLN5 and SLN8 is significant ($p < 0.05$).

active ingredients and also an enhanced patient compliance [10]. Topical drug delivery however, is still a challenge in pharmaceutics and drug delivery due to the difficulties in controlling and determining the exact amount of drug that reaches the different skin layers [11]. The Active Pharmaceutical Ingredient (API) as well as the vehicle's physicochemical behaviour remains the main factors responsible for the drug differential distribution in the skin [12–14].

The bioavailability of naproxen via the percutaneous absorption is poor [15,16] thus different technologies such as the pro-drug approach [6,17,18] and use of penetration enhancers in appropriate vehicles [19] have been adopted to overcome the penetration issue of naproxen through the skin.

Recently, Solid Lipid Nanoparticles (SLN) features have been considered advantageous for topical administration of active substances. The great potential of SLN to improve prednicarbate absorption through the skin was demonstrated [20]. Another recent study reported that triptolide topical anti-inflammatory therapy was favoured by its entrapment in SLN. This strategy guaranteed an improved availability of the drug at the site of action, reducing the contemporary needed dose and thus, dose dependent side effects like irritation and staining [21].

SLNs introduced in 1991 [22], have emerged as an alternative colloidal carriers due to advantages such as improved physical stability, good tolerability, efficient incorporation of lipophilic drugs in the lipid core of the SLNs and ease of scale up and manufacturing [23]. These nanoparticles possess a solid lipid core matrix that is solubilized by surfactants [24].

Puglia et al., showed that SLNs containing naproxen could be used as a platform for prolonged topical delivery to the skin and thus enhancing the anti-inflammatory effect of the drug [25]. They however did not investigate how the changes in HLB of the system using different proportions of binary mixtures of two surfactants with different HLB values during the preparation of the nanoparticles can change the physicochemical properties of SLNs. The aim therefore of the current study was to produce naproxen solid lipid nanoparticles to improve its skin permeation and to fully characterize them. To the best of our knowledge there is no study that has investigated the two faces of HLB in the optimization of SLNs as such this is where the novelty of the present study lies.

2. Materials and methods

2.1. Materials

Naproxen (Nap) was purchased from Alborz bulk Co. (Tehran, Iran). Tween 80 (Samchun Pure Chemical Co., Ltd. Korea), Span 80 (Daejung Chemicals & Metals Co., Ltd. Korea), glyceryl mono stearate (GMS, (Merck Co.,Germany)) were used. Distilled water was purified using a Milli-Q system (Millipore, Direct-Q).

2.2. Preparation of NAP-SLN

Naproxen nanoparticles were prepared using the probe ultrasonication method, which has been used previously for the production of lipid nanoparticles [24]. The mixture of GMS with naproxen was melted at below 100 °C using a heater stirrer. The heated mixture of solid lipid and naproxen was then mixed with 80 ml of pre-heated surfactant solution (Tween and Span mixture in percentages as in Table 1 in 80 ml water) to form a pre-emulsion. The mixture was then sonicated for 10 min at 95 °C using a probe sonicator (Bandelin, Germany). Since this step is carried out at a temperature greater than the melting point of the lipid, at this stage nanoemulsion can be present due to the liquid state of the lipid. The mixture was then immersed in an ice bath instantly after the sonication process finished. This cooling step promoted the formation of the solid lipid nanoparticles. For more details of the composition readers are directed to Table 1.

2.3. Physicochemical characterization

SLNs were characterized in terms of mean particle size, polydispersity index (PDI) and zeta potential (ZP). Briefly, Zeta potential and poly dispersity index (PDI) of the nanoparticle formulations were determined using Zetasizer (Nano ZA, Malvern Instruments, UK). In this method the sample was measured at 25 °C with an angle detection of 90°. The concentration of the samples for analysis on the Zeta Sizer was 20–400 kilo counts per second (KCPS) and the intensity of diffraction was 100,000 counts per second.

2.4. Entrapment efficiency

To determine the entrapment efficiency (EE%) of Nap in the SLNs, the Nap-SLNs were subjected to centrifugation for 90 min at 29,000 rpm (HERMLE, Z36HK, Germany), filtered (pore size: 0.22 μm) and the amount of Nap in supernatant (free drug) was determined by HPLC Agilent 1100 at 230 nm, which was equipped with the Agilent Eclipse XDB-C18 column (5 μm, 4.6 × 250 mm). The mobile phase, composed of 40:20:40 acetonitrile, methanol and acetic acid (1% v/v) was delivered at 0.7 ml/min. The retention time of the drug was 11 min. Drug entrapment efficiency (EE%) was calculated using Eq. (1):

$$EE\% = \frac{W_{initial\ drug} - W_{free\ drug}}{W_{initial\ drug}} \times 100 \quad (1)$$