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Research Article

FORMULATION AND PREPARATION OF FELODIPINE NANOEMULSIONS

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ABSTRACT

The objective of present work was development of felodipine nano emulsion formulations using sesame oil as sole lipid phase by high pressure homogenization technique. A combination of non-ionic surfactants was used based on HLB (Hydrophilic lipophilic balance) values. The resultant nano emulsions were characterized for particle size, zeta potential. The particle size for the optimized nano emulsions was 162.7±8.1 and zeta potential was -37.5±5.2. Percentage drug content was found to be 79.56±1.43%. Centrifugation and freeze – thaw cycling showed no signs of creaming.

Keywords: Nano emulsions, HLB, Felodipine, Sesame oil, Sonication, Pluronic F 68.

INTRODUCTION

Nano emulsions (NE) are a class of emulsions with very small and uniform droplet size, typically in the range of 20-500nm [1]. NEs are not thermodynamically stable, but pass a high kinetic stability. NEs can be used as excellent vehicles in pharmaceutical field for the parenteral, oral, and ocular and transdermal delivery of poorly permeable lipophilic drugs [2]. Felodipine was selected as a model drug for the present study. Felodipine was a calcium chanel blocking agent and used in the treatment of hypertension and angina. Chemically it is 3-ethyl, 5-methy 4- (2,3-dichloro phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

It is practically insoluble in water and highly photosensitive [3, 4]. These properties of felodipine make it suitable for the formulation of NEs. The objectives of present study were formulation development of NEs using sesame oil as lipid phase and to study the effect of HLB values in selecting the non-ionic surfactants for the preparation of NEs and to study the effect of sonication time and quantity of surfactant on properties of NEs.

Felodipine was a gratis sample from Dr. Reddy's Laboratories (Hyderabad, India), Pluronic-F-68, Span-80 (Sigma Aldrich, USA), and sesame oil was purchased from Thiagarajan Agro Products Pvt Ltd, Chennai. All other chemicals are of analytical/HPLC grade and purchased from S.D. Fine Chemicals, India.

A combination of surfactants were selected on the basis of HLB values{Span-80 and poloxamer (PLURONIC-F-68) } and were taken in a beaker , water was added and sonicated for 5mts to obtain a fine dispersion because span-80 is insoluble in water. Oil phase was prepared by dissolving the drug in oil. Both the solutions were combined and stirred with a stirrer for 25 minutes at 6000 rpm to produce a primary emulsion which is then sonicated at various time intervals using probe sonicator (Bandelin Sonoplus, Heinrichstrab 3-4 D-12207, Berlin, Germany) [5].

At first various NEs were prepared using a combination of non-ionic surfactants Poloxamer (HLB value was 29) and span-80 (HLB value was 4.3) at different concentrations of 0.5%, 1% and 1.5%. Their quantities were calculated using method of allegation. To optimize the sonication time, sonication was done at different time intervals of 5, 10, 15 min using probe sonicator (Bandelin Sonoplus, Heinrichstrab 3-4 D-12207, Berlin, Germany). Particle size, zeta potential and Polydispersity index (PDI) were measured for all the formulations with the help of Particle sizer Nano ZS (Malvern Instruments, UK).

The average particle size and polydispersity index were measured by photon correlation spectroscopy (PCI) using a Malvern particle sizer (Nano ZS Malvern Instruments Ltd., UK). The prepared formulations were diluted with triple distilled water to get optimum kilo count per second (kcps) 50 to 200.The diluted NEs were kept in the cuvette with an attached dip cell. The cuvette was placed inside the instrument and the observations were recorded at 90° light scattering angle and temperature was maintained at 25 °C. The PDI represents the uniformity of the particle size and size distribution of the NE (6).

The zeta potential was also measured by using the same instrument with inbuilt software based on the electrophoretic mobility of globules and the Helmholtz-Smoluchowski equation.

$$\text{Zeta potential (Zp)} = 6\pi\upsilon\eta/\varepsilon\chi$$

Where Zp is in volts, υ = migration velocity cm/sec, η = viscosity of the medium in poise, ε = dielectric constant of the external medium, and χ = potential gradient in volts [6].

The selected formulations were centrifuged at 5000 rpm for 5 h and at 10000 rpm for 30 min and were observed for creaming or phase separation.

High energy emulsification technique was employed for the preparation of NEs. Sesame oil was used as sole lipid phase for the present study. Surfactants play a major role in the preparation and stability of NEs. Surfactants form a monomolecular film around the dispersed droplets and there by reduces the interfacial tension and prevent the droplet coalescence. Non-ionic surfactants are not toxic in low concentrations and therefore span-80 and poloxamer were selected.

The required HLB (hydrophilic lypophilic balance) of sesame oil is 7 and it is considered as an important criterion for selection of the surfactants. The right blend of low and high HLB surfactants leads to the formation of a stable nanoemulsion formulation (7, 5). In this study, we selected Span 80 as a surfactant with an HLB value of 4.3 and poloxamer with an HLB value of 29. To determine the optimum concentration of surfactant various NEs were prepared at different concentrations. The optimum surfactant concentration was found to be 1.5%.

Nanoemulsions are not formed spontaneously. High energy input is required in the form of chemical or mechanical energy. The amount of surfactant is also important to form rigid film around dispersed globules. The NEs were not formed when the concentration of surfactant was 0.5%. When the concentration of surfactant was increased from 0.5% to 1%, NEs were formed and the particle size was 231.8nm and further increase in surfactant concentration i.e from 1 to 1.5% the particle size was reduced from 231.8 to 162.7 nm.

However use of excess amount of emulsifier can cause decrease in entrapment efficiency, burst release and formation of other colloidal species such as liposomes and micelles and may even cause toxic effects. (8). Therefore for the present study a total quantity of 1.5% of span-80 and poloxamer (pluronic F-68) was found to be optimum. Initially all the formulations were sonicated at different time intervals of 5, 10 and 15 minutes. But visible oil globules were appeared on the surface of the NEs. So, first the oil phase and

aqueous phase were mixed and homogenized for 25 minutes at 6000 rpm using homogenizer to form a micro emulsion and sonicated at the above said intervals to reduce the dispersed phase globules to nano size. When the sonication time was increased from 5 to 15 minutes the particle size was decreased. With 1% surfactant concentration the optimum sonication time was found to be 15 minutes and with 1.5% concentration of surfactant the optimum sonication time was found to be 10 minutes. In all the formulations the PDI was in the range of 0.180 to 0.346, which suggests a narrow particle size distribution.The zeta potential is a measure of the stability of NEs.

The surface of the dispersed droplets studded with charged groups. This produces a surface charge on the droplet which in turn causes the formation of diffuse double layer. The potential produced by the double layer creates a repulsive effect between the oil droplets and hinders coalescence. This repulsive electric potential cannot be measured directly; however the related quantity that is zeta potential can be determined. To ensure electrostatic stability of particulate formulations should have a value of zeta potential greater than + 30 mv or lower than – 30 mv (9). In the present study the zeta potential for all the formulations was found to be in the range of -28.8 to -43.3 which indicates that the resultant NEs were stable. The stability of NEs was confirmed by centrifugation which shows no phase separation.

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