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Comparative evaluation of pharmacokinetic parameters between a pure nisoldipine suspension and a nisoldipine-loaded bilosome suspension

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Abstract

Bilosomes are nanocarriers that contain bile salts in their vesicular bilayer, thereby enhancing their flexibility and durability in the gastrointestinal tract. Unlike conventional vesicular systems they provide distinct advantages such as streamlined manufacturing procedures, cost efficiency, and improved stability. The main objective of this study was to attain a comparison of the pharmacokinetic parameters of nisoldipine (NSD) after administering an ordinary NSD suspension and an NSD-loaded bilosome suspension. The study used 60 Swiss albino rats weighing 200±15 g and divided into two groups (n=30 each). A dose of 2.2 mg/kg of NSD was administered from the ordinary NSD suspension to the rats of the first group and the same dose of NSD-loaded bilosome suspension was administered to the rats of the second group. NSD levels were determined in the rat plasma by using high-performance liquid chromatography. Our results showed that the C_{max}, the T_{max}, and the AUC_{0-36} were 51.47±0.94 ng/mL, 2±0.3 h, and 323.33±21 ng×h/mL for the pure suspension, and 116.41±1.22 ng/mL, 4±0.7 h, and 916±64.09 ng×h/mL for the bilosome suspension, respectively. The maximum concentration was significantly different between the pure and the bilosomal preparation (P<0.05), while the relative bioavailability of the pure suspension was 2.9 times that of the bilosomal suspension, 36 h after a single-dose NSD administration. In conclusion, the prepared bilosomal suspension enhanced the bioavailability of NSD, and could be considered as a vital delivery system.

KEYWORDS
bilosomes; nisoldipine, pharmacokinetics, animal study, bioavailability

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1. INTRODUCTION

The oral route is the most prevalent and favored method of administering drugs, due to its ease and high level of patient adherence. Nevertheless, administering the drug through this method frequently leads to a less than ideal therapeutic outcome due to the drug's limited ability to dissolve in gastrointestinal fluids, inadequate ability to pass through the gastrointestinal barrier, and significant initial metabolism [1].

Bilosomes are nanocarriers that contain bile

salts in their vesicular bilayer, thereby enhancing their flexibility and durability in the gastrointestinal tract (GIT) [2,3]. The resistance to enzymatic degradation in the GIT is attributed to the presence of bile salts in the vesicle membrane, which boost penetration and improve the effectiveness of oral delivery. Non-ionic surfactants, such as those in the Span family, are commonly employed in the creation of bilosomes.

Predicting plasma concentration-time curves is possible with the help of the drug's physicochemical properties in physiologically-based pharmacokinetic models. Validating the model with publicly-available clinical pharmacokinetic data is a must before implementation [4].

Nisoldipine (NSD) is a compound derived from dihydropyridine that functions as a blocker of calcium channels. NSD undergoes presystemic metabolism, resulting in just 5% of it being utilized by the body. Additionally, it exhibits a binding affinity to CYP3A and P-glycoprotein [5].

The main objective of this study was to create an enhanced formulation for NSD by using bilosomes, with the goal of improving its oral bioavailability as compared to a regular NSD suspension.

2. MATERIALS AND METHODS

Materials: The acquisition of NSD was made from Lee Chemicals, India. Cholesterol, surfactant Span 60, and bile salt sodium deoxycholate were obtained from HyperChem, India. All the chemicals and solvents used in this study were of analytical grade.

In vivo pharmacokinetic studies: This study employed 60 male Swiss albino rats, aged three months, with an average weight of 200±15 g. The rats were housed in the animal facility of the Research Centre for Cancer Research and Medical Genetics, Baghdad, Iraq, under controlled circumstances of a constant room temperature of 25°C±1°C and a 12-h light/dark cycle. The rats were provided unrestricted access to both food and water. The *in vivo* experiments performed on the rats were authorized by the Research Ethics Committee for Experimental Investigations, College of Pharmacy, Baghdad University, Iraq, under the protocol number RECAUBCP262022A.

Dosing protocol: Before administering the oral medication, two groups of rats (n=30 each) were subjected to an overnight fast lasting more than 12 h. Rats were orally administered the drug-loaded bilosome formulation (NSD-loaded bilosome suspension) or the control formulation (pure NSD powder suspension) using an oral gavage at a dose of 2.2 mg/kg. During administration, both groups were administered ketamine at a dose of 80 mg/kg, and each animal also received xylazine at a dose of 10 mg/kg [6].

Each sampling was timed, and a single dose was administered to both groups in order to assess the relative bioavailability of the pure NSD suspension and of the NSD-loaded bilosome suspension. A total of 5 mL of blood was acquired from the myocardium through piercing at predefined time intervals ranging from 0 to 36 h. EDTA-treated tubes were used in order to collect blood samples from the rats, which were then promptly separated. Plasma samples were obtained by centrifuging the blood samples (Hettich Zentrifugen EBA 20, Germany) at a speed of 4,000 rpm for a duration of 10 min. Plasma samples were collected from the liquid portion, transferred into Eppendorf tubes, and preserved in the freezer for subsequent investigation. A modified and confirmed approach was used in order to evaluate the samples of plasma by using reversed-phase high-performance liquid chromatography (RP-HPLC).

This study measured the maximum plasma concentration (C_{max}) of the medication as well as the time it took to reach C_{max} (T_{max}). The $AUC_{0\text{-}36}$ and $AUC_{0\text{-}\infty}$ were determined by calculating the integral of the plasma concentration-time curve from time 0 to 36 h and from 0 to infinity, respectively.

Statistical analysis: The results were presented as mean values with their standard deviation (±SD; n=3). A difference was deemed statistically significant if the *P*-value was less than 0.05. The pharmacokinetic parameters, namely C_{max}, T_{max}, and $AUC_{0\text{-}36}$, were subjected to statistical analysis by means of a Student's *t*-test [7]. The equation employed so as to evaluate the relative bioavailability (F) of NSD was as follows:

$$\frac{\text{AUC bilosomal suspension} \times \text{dose free drug suspension}}{\text{AUC free drug suspension} \times \text{dose bilosomal suspension}} \times 100$$

3. RESULTS

The calibration curve was generated by following the recommended protocol for the spiking plasma, by using a certain solution of NSD with a specified concentration. The HPLC analysis revealed the presence of endogenous components in the blank plasma chromatogram, with a retention time of 1.9. The spiked sample's chromatogram exhibited clear differentiation between NSD and nimodipine, with NSD having a retention time (Rt) of 5.79 min and nimodipine showing a signal at 3.57 min.

A validated HPLC method was employed to quantify the quantity of NSD in the plasma of the rats. All validation parameters met the conventional criteria. Six concentrations were employed in order to evaluate the linearity of the method and

determine the lower limit of detection, which existed at 1 ng/mL [8].

The oral NSD-loaded bilosome suspension was assessed for its relative bioavailability in comparison to the oral free NSD suspension. Figure 1 displays the average concentration of the drug in the rat plasma *versus* time after administering orally a free drug suspension and a drug-loaded bilosome suspension.

The statistical analysis employing a *t*-test indicated that the concentration (C_{max}) and the time (T_{max}) required in order to achieve the highest effect were 51.47±0.94 ng/mL and 2±0.3 h for the free NSD suspension and 116.41±1.22 ng/mL and 4±0.7 h for the NSD-loaded bilosome suspension, respectively. Our results indicate a statistically significant disparity between these values (P<0.05). Each of these numbers was tested at the significance level, and each relate to three separate measurements [9].

The $AUC_{0\text{-}36}$ (area under the curve from 0 to 36 h) for the free NSD suspension was 323.33±21 ng×h/mL, which was considerably lower (P<0.05) compared to the $AUC_{0\text{-}36}$ for the NSD-loaded bilosome suspension (916±64.09 ng×h/mL). The comparative bioavailability of the two preparations indicated that the bilosomal suspension can exert a 2.9-fold greater availability (P<0.05) than the pure drug suspension at 36 h after a single-dose administration.

4. DISCUSSION

The enhanced absorption of NSD from the bilosomal suspension can be related to the successful encapsulation of NSD within the bilosomes that are in the nano-size range and are primarily composed of surfactant (Span 60). This surfactant not only enhances solubility, but also acts as a penetration enhancer. In addition, bilosomal vesicles contain bile salts that confer elasticity to the vesicles, increase permeability, and provide resistance to physiological bile salts in the GIT. Moreover, the vesicles' negative charge facilitates the uptake of drugs by the M-cells of Peyer's patch in the intestine, and improves drug absorption through the pathway of intestinal lymphatic transport, thereby bypassing the initial drug processing in the liver [10].

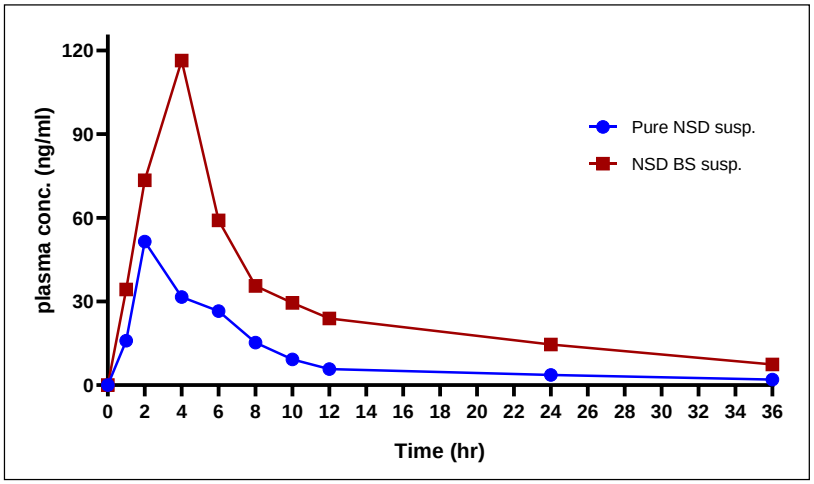

Figure 1. Rat plasma concentrations of nisoldipine (NSD) measured after administering the drug orally in the form of a free drug suspension and in the form of a NSD-loaded bilosome (BS) suspension.

5. CONCLUSION

Ultimately, the generated NSD-loaded bilosome suspension has a much higher relative bioavailability compared to the free NSD solution. Consequently, it is deemed as a more advantageous dosing form for the administration of NSD in the treatment of hypertension. In future research, the use of bilosomes as a delivery mechanism should be considered as a possible method to increase the bioavailability of NSD.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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