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Naproxen-phospholipid complex, a new vesicular drug delivery system: Design, development, and evaluation

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ABSTRACT

This study was aimed at preparing and assessing the Naproxen-phospholipid complex (NP-PL) as a vesicular drug delivery system prepared by solvent evaporation method. Attenuated total reflection (ATR) spectroscopy was used to confirm the interaction, while a dissolution study was used to compare the dissolution profiles for the NP drug, the NP-PL complex, and the marketed NP suspension. Results revealed that the ATR spectra showed some changes that confirm the complexation between the PL and NP, and better dissolution behavior was shown by the NP-PL pharmacosomes compared to the NP suspension and the pure NP, which indicates that the potential of making a phospholipid complex with an improved dissolution profile of Naproxen was investigated and a successful NP-PL pharmacosomes was prepared. ATR data confirmed NP-PL complex formation. *In-vitro* dissolution profiles of NP pharmacosomal dispersion showed improvement over marketed NP and pure NP.

Keywords: naproxen, naproxen-phospholipid complex, phospholipid, solvent evaporation method

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INTRODUCTION

Phospholipids (PL) are one of the most common amphiphilic molecules that have both hydrophobic and hydrophilic regions, In the presence of water, phospholipids arrange themselves into one or more concentric bilayers (vesicles)[1]. Complexes of drugs with lipids that have a functional group capable of interacting with the functional group in the drug, for example, phosphatidylcholine, have a phosphate functional group that can interact with Naproxen (NP) to form pharmacosomes (vesicles) that show several advantages, such as enhancing orally administered drug bioavailability and reducing the toxicity of drugs[2,3]. Naproxen (NP) is from the profen family (2-arylpropionic acid) of the non-steroidal anti-inflammatory drugs. Naproxen has good lipid solubility which make it insoluble in water and causes some problems in dissolution[4]. The oral administration of Naproxen is available as suspension or tablet (immediate and extended release) dosage form[5]. From the primary adverse effects for naproxen is gastro-intestinal ulcers[6,7]. Phospholipids can interact through hydrogen bond and/or van der Waals forces with drug molecules that have an active hydrogen atom[8]. The aim of this study is to prepare and assess of Naproxen-phospholipid complex (NP-PL) as vesicular drug delivery system.

MATERIALS AND METHODS

Materials

Lipoid S 100, which is a soybean phosphatidylcholine with a purity of 94%, was obtained from Lipoid GmbH, Germany. The pure Naproxen provided by Sigma-Aldrich, Germany, and the purity of NP were determined and assessed by UV lambda max and melting point methods. Reagents and solvents used are commercially available in analytical grade.

Preparation of Naproxen-phospholipid complex

Naproxen-phospholipid complex (NP-PL) was prepared by using the solvent evaporation method. Highly purified (94%) soybean phosphatidylcholine and Naproxen (NP) were dissolved in 30 mL of dichloromethane, which is used as a solvent due to its good solubility for both naproxen and lipoid S100 and also because it is considered a good option for the solvent evaporation method due to its low boiling point. The components were placed in a round bottom flask in a ratio of 1:1 mole (50 mg Naproxen with 157 mg PL), which has been proven in previous research to be the best ratio for complexation.

Three hours of stirring at 35°C were done to the mixture by a magnetic stirrer, then a rotary evaporator with low pressure used for solvent removal. The obtained lipid film retained in a desiccator for a day[9].

Attenuated total reflection (ATR)

The ATR analysis of pure NP, PL, NP-PL were carried out with a Bruker Alpha-P ATR FTIR, Germany.

Preparation of Naproxen vesicular systems

The hydration of the obtained lipid film that contain NP-PL by a solution of phosphate buffer saline (PBS, pH 7.4) at 55±2°C resulted in pharmacosomal dispersion[10].

Investigation by transmission electron microscopy (TEM)

A TEM instrument (Philips, Netherland) was used to investigate the NP-PL Pharmacosomal dispersion. 1% phosphotungstic was used to stain a little amount from the dispersion that placed on carbon grids that coated with copper[11].

In-vitro dissolution study

A rotating paddle dissolution apparatus type II containing phosphate buffer (pH 7.4) with a volume of 900 mL at speed 100 rpm was used to compare the dissolution behavior of NP pharmacosomal dispersion, NP suspension, and the pure NP powder. Each formula containing 125 mg of Naproxen[12] the concentration of the marketed NP used is 25mg/ml and a 5 ml of the product were used to obtaind the 125mg of NP. The used media was preconditioned and maintained at a 37 °C. At a proper time interval, 5 mL sample were drawn then replaced with a new dissolution medium. The filtration of the samples was done through a 0.45 μm filter syringe. A UV-Visible spectrophotometer was used to determine the drug content of the solution.

RESULTS and DISCUSSION

ATR of the prepared Naproxen-phospholipid complex

The prepared phospholipid complex of Naproxen by the solvent evaporation method were characterized by ATR to confirm the interaction between the two molecules. The ATR spectra of NP, PL, Naproxen-phopholipid complex (NP-PL) are displayed in Figure 1. Significant changes detected in the spectrum of NP-PL, the Naproxen OH stretching band absorption peak which occur at (3145 cm^{-1}) was shifted to lower wavenumber (3008 cm^{-1}), the stretching band of the C=O (1680 cm^{-1}) of NP was moved to lower wavenumber (1633 cm^{-1})[13]. Additionally, the P=O stretching band absorption peak of the of PL (1251 cm^{-1}) have been moved to higher wavenumber (1262 cm^{-1}). An interaction between the polar part of the PL (phosphate) and the carboxyl group of NP might be suggested by the obtained results[14]. The chemical structure of NP and PL were illustrated in Figure 2.

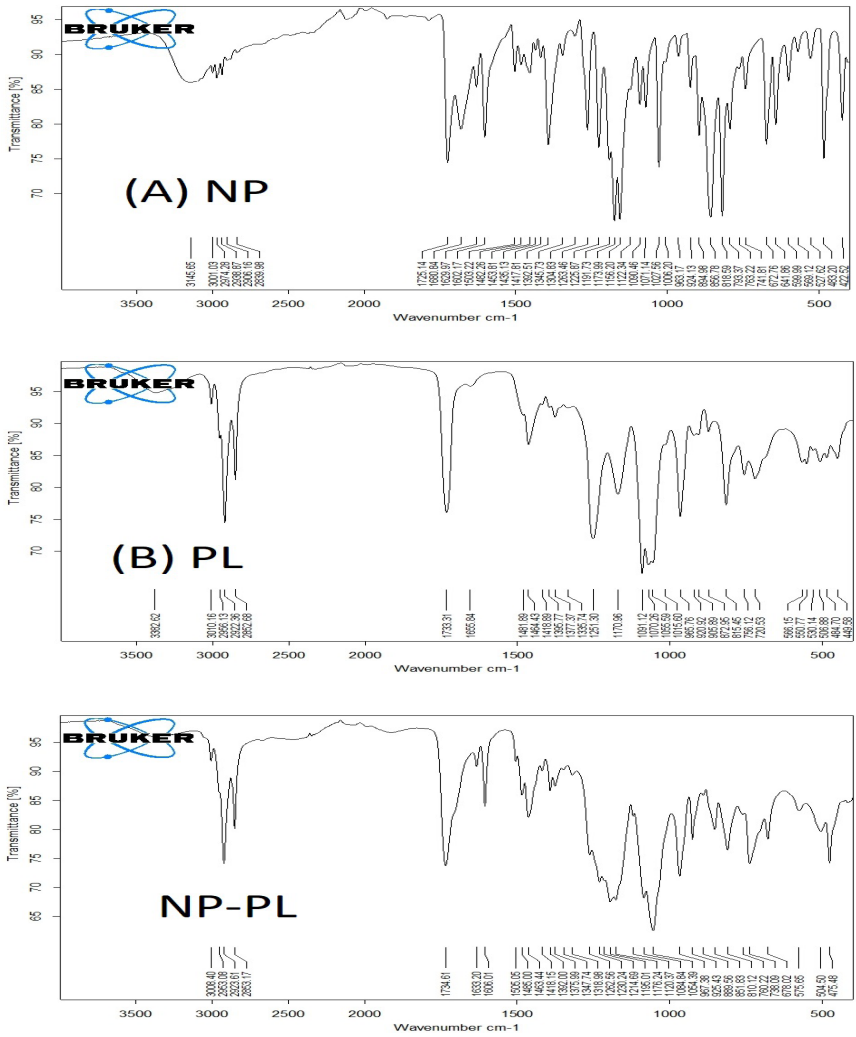
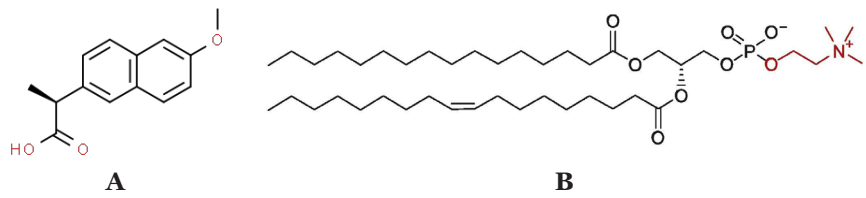


Figure 1. ATR spectra of (A) NP (B) PL (C) NP-PL



A **B**

Figure 2. Chemical structures of (A) Naproxen, (B) phospholipid

Examination using transmission electron microscopy (TEM)

The Naproxen pharmacosomal dispersion was examined by TEM. Figure 3 show the TEM photographs that revealed spherical structures, these structures indicating vesicle formation.

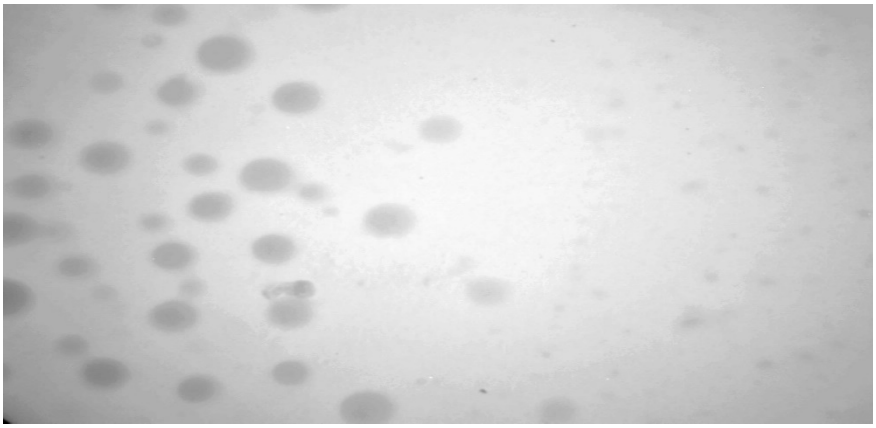


Figure 3. TEM photographs of Naproxen pharmacosomal dispersion

In-vitro dissolution study

The dissolution behavior of Naproxen pure powder (NP), NP pharmacosomal dispersion in comparison to marketed NP suspension in phosphate buffer (PB) pH 7.4 are shown in Figure 4. NP-PL dispersion show higher dissolution profile than pure NP and marketed NP suspension, one of the factors that the dissolution study depend on is the solubility of compounds. So, it will give an estimation for the enhancement in solubility and the rapid and enhanced dissolution rate of pharmacosomal dispersion in the dissolution behavior could be attributed to the role of lipid vesicles by decreasing the surface interfacial tension[15].

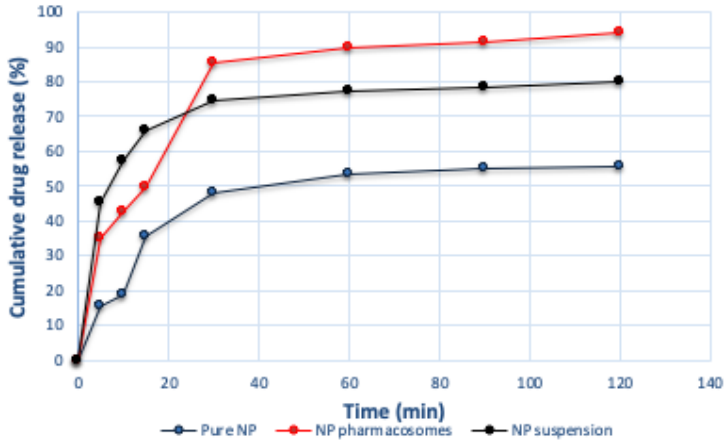


Figure 4. Dissolution profile of pure NP, NP pharmacosomal dispersion, and marketed NP suspension in phosphate buffer 7.4

A successful Naproxen-phospholipid complex (pharmacosomes) was prepared using solvent evaporation method and the ATR data confirmed NP-PL complex formation and *in-vitro* dissolution profile of NP pharmacosomal dispersion showed an improvement over marketed NP and pure NP.

STATEMENT OF ETHICS

Ethical approval was not required to perform this study.

CONFLICT OF INTEREST STATEMENT

The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed equally for this work.

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Not applicable.

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