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Research Article

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Synthesis of Naproxen pro-drugs for enhanced transdermal absorption

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ABSTRACT

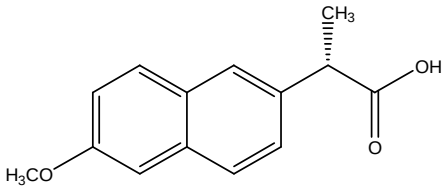
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as Naproxen have been used for a long time for the treatment of acute and chronic inflammation conditions. However, the oral administration of NSAIDs for a long time can cause gastric mucosal damage, which may result in ulceration and bleeding. Therefore, the development of a transdermal drug delivery (TDD) system of NSAIDs is of a great interest as it decreases GIT side effect and provides a constant release of drug in a determined period of time. Moreover, one of the important parameters of TTD is improving the permeability of the drug through human skin, since the stratum corneum layer of the epidermis prevents the permeability of various drugs and the naproxen in particular. In this present paper, we have successfully synthesized and characterized various ester derivatives of naproxen (methyl, ethyl, propyl, butyl, pentyl and hexyl esters) that have more suitable physicochemical properties for TDD and the butyl ester derivative has been formulated into liquid formulation for topical administration. The formulation was tested for stability according to ICH guidelines. No change in the initial appearance was observed during three months of study at room temperature & at 40 ℃. The assay and pH were within the international standard limits during the period of the study. So, stable topical formulation of naproxen ester has been obtained.

Keywords: Naproxen, Ester prodrugs, Topical formulation, Transdermal Absorption.

INTRODUCTION

The vast majority of designed drugs are administered by the parenteral or oral routes. However, their physico-chemical properties and stability profile hampered their topical administration. This is due to the barrier characteristics of the skin which does not allow the easy penetration of substances through it.

Naproxen [(+)-(S)-2-(6-methoxynaphthalen-2-yl)propanoic acid] figure 1, is a potent non-steroidal anti-inflammatory drug (NSAID) that is often used for the treatment of acute and chronic inflammation conditions, musculoskeletal disorders, primary dysmenorrhoea, fever and also in the management of mild pain [1]. However, the systemic use of Naproxen shows various adverse effects such as epigastric distress, gastric ulceration, hemorrhage and iron-deficiency anemia [2]. These side effects are explained by two mechanisms, the first one is due to the direct contact and local irritation produced by the carboxylic acid group of the molecular structure of the Naproxen [3], so the utilization of prodrug can temporarily mask the carboxylic acid group of the Naproxen and decrease the gastric side effects [4]. The second mechanism is referred to the inhibition of the prostaglandin synthesis [3].



Naproxen

Figure 1. Chemical structure of Naproxen

One of the interesting approaches, to overcome the NSAIDs side effects is the transdermal drug delivery system (TDD) of the topical anti-inflammatory agents. TDD is one of the most attractive routes of drug administration since it has several advantages including: the ease of application, patient compliance, elimination of the gastrointestinal tract absorption variables, avoid first pass metabolism, improve patient compliance and reduce drug plasma concentration fluctuations [5-8].

As the physico-chemical properties of the drug have a great importance in the crossing of the stratum corneum [9], the optimum properties can be achieved through the prodrug strategy. Ester is one of the most common approaches to develop prodrugs that can be hydrolyzed to the active ingredient by the action of different esterases [10]. In this present work, we have successfully synthesized various alkyl ester prodrugs of Naporxen to develop new topical formulation; the stability of the formulation was then evaluated under normal and stress conditions[11].

EXPERMINTAL SECTION

Materials:
Naproxen powder was obtained as a gift from Birzeit Pharmaceutical Company (Ramallah, Palestine). All the reagents that were used in chemical synthesis and the formulation were of analytical grade and were purchased from reliable resources. The used reagents are: Absolute ethanol, Butanol, n-Hexane, Ethyl Acetate, Sodium Hydroxide and Isopropyl Alcohol, 1-Propanol, Pentanol, Hexanol, Sulfuric acid, Isopropyl Palmitate, Silica and Anhydrous Magnesium Sulfate.

Instrumentation:
FTIR Spectrometer (Nicolet iS5, Thermoscientific Co.) was used for identification of the esters. Rotary Evaporator (VV2000 OB2000, Heidolph) was used for solvent drying. A sensitive weighing balance (Adventurer, OHAUS Corporation) was used. UV Lamp (Model UVGL-58,Mineralight® Lamp, Upland, USA) was used to check TLC. Spectrophotometer (7315 Spectrophotometer, Jenway) was used in the stability evaluation of the formulation.

Methodology:
A series of Naproxen alkyl esters were synthesized by carrying out esterification reactions with methanol, ethanol, propanol, butanol, pentanol and hexanol. The obtained esters were purified using column chromatography (Hexane: Ethyl acetate), while naproxen Butyl ester was purified by crystallization. All the Esters were also characterized using TLC, melting point, FTIR spectroscopy and UV-Vis spectrophotmetry.

Formulation of topical solution was carried out for Naproxen butyl ester by dissolving the active ingredient in Isopropyl Alcohol (20 ml), heat was applied when needed. The obtained solutions were filled up to 100 ml with Isopropyl Palmitate. The stability tests for the formulation was carried out using a previously validated UV analytical methods for Naproxen and its ester derivatives [12].

General Procedure for Esterification of Naproxen
Naproxen (2.302 g, 10 mmoles) was placed in 250 ml round bottom flask; 20 ml Butanol and 0.5ml of concentrated H_2SO_4 was added. The obtained solution was kept under reflux while mixing using a magnetic stirrer for one night. The completion of the reaction was checked by TLC, using a mixture of 1:1 hexane and ethyl acetate as a mobile phase. After the solution was cooled at room temperature, it was neutralized using sodium bicarbonate. Butyl ester was extracted in a separatory funnel using ethyl acetate. The organic phase was dried using anhydrous Magnesium

Sulfate. Naproxen Butyl ester was purified by crystallization with hexane and characterized by TLC, melting point and FTIR spectroscopy. [13]

Formulation of Naproxen & Butyl-Naproxen Topical Solutions:

Naproxen Topical solution:

Naproxen (1 g, 4.35 mmol) was placed in a 100 ml beaker, 20 ml Isopropyl Alcohol was added to dissolve Naproxen and heat was applied gently. The obtained solution was placed in a 100 ml graduated cylinder and the volume was completed to 100 ml with Isopropyl Palmitate. The final product was then transferred into a proper bottle container. (**Table 1**)

Butyl Naproxen topical solution:

Butyl-Naproxen (1 g, 3.50 mmol) was placed in a 100 ml beaker, 20 ml Isopropyl Alcohol ws added to dissolve Butyl-Naproxen and heat was applied gently, the obtained solution was placed in a 100 ml graduated cylinder and the volume was completed to 100 ml with Isopropyl Palmitate. The final product was then transferred into a proper bottle container, (**Table 1**).

Table 1. Formulation of Naproxen & Butyl-Naproxen topical solutions

	Formula 1	Formula 2
Naproxen	1 g	---
Butyl-Naproxen	---	1 g
Isopropyl Alcohol	20 ml	20 ml
Isopropyl Palmitate	Up to 100 ml	Up to 100 ml

Stability evaluation of topical solutions

Samples of naproxen and butyl ester were filled in amber glass bottles. These samples were then subjected to stability studies according to ICH guidelines [14]. The samples were scheduled for stability evaluation at a time interval of 0, 3, 6, 9, and 12 months. Some of the samples were stored at room temperature (RT) and were kept at 25°C ±2 °C. Additional samples were subjected to accelerate stability study and stored at 40°C ±2 °C; these samples were tested at time 0, then at 1, 2 and 3- month intervals. Samples were evaluated for their physical appearance, pH, and precipitation and assayed using validated assay procedures to evaluate the stability of liquid solutions[15].

RESULTS AND DISCUSSION

A series of alkyl alcohols were successfully transformed into the corresponding naproxen esters. The TLC examination of all the esterification reactions showed a single new spot with R_f different than Naproxen R_f and the corresponding alkyl alcohol. Figure 2 & Table 2.

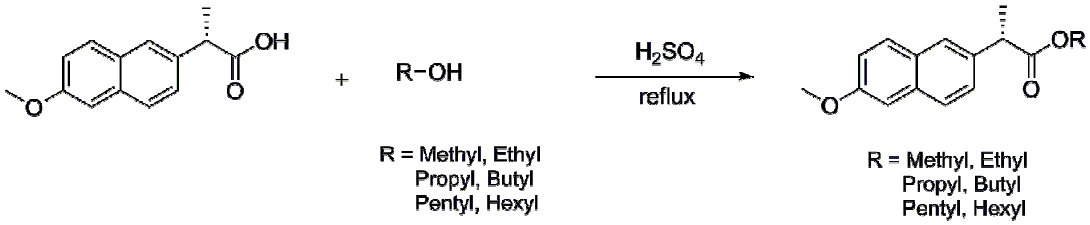


Figure 2. Synthesis of Naproxen Esters

Table 2. R_f value of Naproxen & synthesized butyl ester

Compound	R_f Value (Hex: EtOAc, 1:1)
Naproxen	0.25
Methyl-Naproxen	0.28
Ethyl-Naproxen	0.32
Propyl-Naproxen	0.43
Butyl-Naproxen	0.5
Pentyl-Naproxen	0.57
Hexyl-Naproxen	0.66

The Naproxen butyl ester was purified by crystallization to obtain a white powder with melting point = 45°C. Furthermore, it was characterized using FTIR as reported in Table 3.

Table 3. FTIR characterization of Butyl-Naproxen

Product	FTIR	
Naproxen	υ C=O stretch	1726
	υ OH stretch	3200
	υ OH bend	1419
Naproxen butyl ester	υ C=O stretch	1720
	υ OH stretch	------
	υ OH bend	------

Regarding the stability test of the topical formulations of Naproxen and Naproxen butyl ester, it was conducted according to the ICH guidelines. The tested samples showed no sign of change in color, precipitation or any undesired physical change. The pH was constant during the period of the study. The percentage amount of Naproxen & Naproxen butyl ester was within the accepted range as reported in Table 4.

Table 4. Stability Studies of Naproxen & Butyl-Naproxen topical formulation

			Time(months)	
	Temp	**1**	**2**	**3**
Naproxen	25°C	98-99%	98-99%	98-99%
	40°C	98-99%	98-99%	98-99%
Butyl-Naproxen	25°C	98-99%	98-99%	98-99%
	40°C	98-99%	98-99%	98-99%

CONCLUSION

Alkyl Naproxen esters were successfully synthesized using an acid catalyzed esterification reaction. The FTIR for butyl ester of Naproxen showed new signals; characteristic of ester group.

Topical solutions for naproxen and its butyl ester were successfully formulated. The topical formulation was stable during three months of stability studies. The kinetics of hydrolysis at different pH should be carried out in order to evaluate the necessary time to release the drug from the ester. Moreover, comparative transdermal absorption between the esters and the parent drug should be carried out using transdiffusion.

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