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SYNTHESIS AND FORMULATION OF IBUPROFEN PRO-DRUGS FOR ENHANCED TRANSDERMAL ABSORPTION

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ABSTRACT

Objectives: The aim is to synthesize ibuprofen prodrugs that have more suitable physicochemical properties and formulate them into a liquid formulation for topical administration. The transdermal delivery (TDD) is one of the most attractive routes for drug administration as it eliminates the GIT absorption variable, improves patient compliance and also reduces drug plasma fluctuations. However, TDD only drugs with suitable physico-chemical properties can be absorbed. The oral administration of NSAIDs for a long time can cause gastric mucosal damage, which may result in ulceration and bleeding. Thus, the development of a TDD of NSAIDs is of great interest as it decreases GIT side effects

Methods: The synthesis of ibuprofen alkyl esters was carried out by esterification reactions with methanol, ethanol, propanol, butanol, pentanol and hexanol. The formulated samples were then subjected to stability studies according to ICH guidelines.

Results: We have successfully synthesized and characterized various esters of ibuprofen. Moreover, ibuprofen butyl ester has been prepared as topical solutions. The formulated TDD was tested for stability according to ICH guidelines and the results showed no changes in the initial appearance during three months of study at room temperature & at 40 °C.

Conclusion: The assay and pH were within the pharmacopeial limits during the period of the study. In conclusion, stable topical formulation of Ibuprofen esters was obtained.

Keywords: Ibuprofen, Prodrugs, Transdermal Drug Delivery.

INTRODUCTION

TDD is one of the most attractive routes of drug administration; since it meets both ease of application and patient compliance [1].

In recent years, many TDD products were developed due to the high number of advantages of this route such as: eliminating of the gastrointestinal tract absorption variables, avoiding first pass metabolism, improving patient compliance and reducing drug plasma concentration fluctuations [2].

Only drugs with suitable physico-chemical characteristics can be good candidates for percutaneous absorption [3-5]. This is due to the barrier characteristics of the skin which does not allow easy travel of substances through it. In order for drugs to be good candidates for percutaneous absorption they must have suitable physico-chemical properties such as a small molecular weight, pKa, melting point and partition coefficient [2]. The pKa of the drug has an importance by influencing many biopharmaceutical characteristics. In fact, this parameter affects the lipophilicity, solubility, protein binding and permeability of the drug [6]. Melting point is also an important parameter the lower it is the better the solubility [2]. Partition coefficient of the drug affects absorption. Overall, the most suitable drugs for topical route are the ones with the most balanced lipid/water partition coefficient [2]. Drugs with higher partition coefficient values are very lipophilic and therefore they do not readily pass from the stratum corneum into the water-rich viable tissue. On the other hand, drugs with low partition coefficient values are very hydrophilic that they cannot pass the lipid-rich layers of the skin. Accordingly, modifying K through synthesis of prodrug will influence percutaneous absorption.

NSAIDs, are a group of chemical agents that differ in their antipyretic, analgesic and anti-inflammatory activities [7, 8]. They are also commonly used in inflammatory conditions and mild to moderate pain. Systemic use of NSAIDs shows some adverse effects including: epigastric distress, ulceration, and hemorrhage and iron-deficiency anemia [9]. Other side effects were observed such as:

nausea, vomiting, constipation, diarrhea, headache, dizziness, rash and kidney failure. Ibuprofen is one of the most used NSAIDs. Chemically, it belongs to the propionic acid class of NSAIDs (fig. 1).

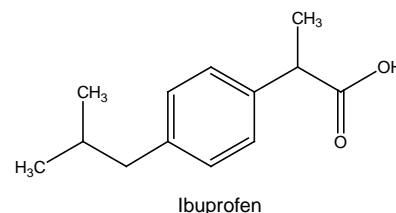


Fig. 1: Chemical structure of Ibuprofen

Topical preparations of Ibuprofen are available in gel forms and they show benefits to the patient by reducing the adverse side effects that may arise after oral or parenteral drug administration. However, topical delivery may face difficulties in maintaining effective concentrations due to its poor skin permeability [10-14].

Stability tests of pharmaceutical formulation are carried out to determine the shelf life and utilization period for a drug or a pharmaceutical drug product. These tests show the ability of a drug substance or product to retain its chemical, physical, microbiological and biological properties within specified limits of packaging and storage conditions. Recently, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established to achieve greater harmonization in the application of technical guidelines and requirements for product registration, which results in a more safeguards on quality, safety, efficacy and regulatory obligations to protect public health. Accordingly, ICH has set guidelines for stability testing of a drug or a drug product. According to these guidelines, the world is divided into five zones based on defining the prevalent annual climatic conditions for the purpose of worldwide stability

testing. In general, samples of drug products for stability testing should be stored according to the storage conditions and testing intervals. In this study we synthesized a series of novel prodrugs for Ibuprofen and formulate it in topical preparations. The formulated prodrug was then evaluated for its stability in accordance to ICH guidelines.

MATERIALS AND METHODS

Materials, Chemicals and instruments

Ibuprofen powder was obtained as a gift from Birzeit Pharmaceutical Company (Ramallah, Palestine). The other reagent that were used in chemical synthesis and the formulation were of analytical grade and were purchased from reliable resources these reagents includes the following: 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.

FTIR Spectrometer (Nicolet iS5, ThermoScientific Co.) was used for identification of the esters. Rotary Evaporator (VV2000 OB2000, Heidolph) was used for solvent drying. The 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.

General procedure for esterification of Ibuprofen

Synthesis of ibuprofen alkyl esters was carried out by esterification reactions with methanol, ethanol, propanol, butanol, pentanol and hexanol. The obtained esters were checked using TLC under the UV lamp. The ibuprofen esters were purified using column chromatography. Esters were then characterized by TLC and FTIR spectroscopy.

One mmole (2.06 g) of Ibuprofen was placed in 250 ml round bottom flask to which 20 ml of the corresponding alcohol were added. 0.5 ml of concentrated H₂SO₄ was added to the above solution to catalyze the esterification reaction. The obtained solution was maintained under reflux and mixing using a magnetic stirrer for one night. The completion of the reaction was checked using TLC, using a mixture of 1:1 ethyl acetate and hexane as a mobile phase. After the solution was cooled at room temperature, it was neutralized using sodium bicarbonate solution. Ethyl ester was extracted using a separatory funnel using ethyl acetate.

The organic phase was dried with anhydrous Magnesium Sulfate then evaporated using a Rotary Evaporator. After that, column chromatography was used to isolate the pure product, using silica gel, n-Hexane and ethyl acetate in a ratio of 7:1 as a mobile phase. Furthermore, the obtained prodrugs were characterized for its physical appearance and melting point.

Calculation of Log P

The log P values were calculated using Crippen's fragmentation in the ChemBioDraw Ultra 11.0 software[15].

Formulation of Ibuprofen & Butyl-Ibuprofen Topical Solutions

Ibuprofen topical solutions

Ibuprofen (1 gm) was placed in a 100 ml beaker; 10 ml Isopropyl alcohol was added to it to dissolve Ibuprofen. The obtained solution was placed in a 100 ml graduated cylinder and filled up to 100 ml with Isopropyl Palmitate. The final product was subsequently transferred into a proper bottle container. (table 1).

Table 1: formulation of Ibuprofen & Butyl-Ibuprofen topical solutions

	Formula 1	Formula 2
Ibuprofen	1 gm	---
Butyl-Ibuprofen	---	1 gm
Isopropyl Alcohol	10 ml	10 ml
Isopropyl Palmitate	Up to 100 ml	Up to 100 ml

Butyl-Ibuprofen topical solutions

Butyl-Ibuprofen (1 gm) was placed in a 100 ml beaker. 10 ml Isopropyl Alcohol were added to dissolve Butyl-Ibuprofen. The obtained solution was placed in a 100 ml graduated cylinder and filled up to 100 ml with Isopropyl Palmitate. The final product was then transferred into a proper bottle container. (table 1)

Stability of topical solutions

The formulated samples of Ibuprofen and butyl ester were filled in amber glass bottles. These samples were then subjected to stability studies according to ICH guidelines. The samples checked at time interval of 0, 3, 6, 9, and 12 months. One prepared formulations were stored at room temperature (RT) at 25 °C ± 2 °C, and an additional samples were subjected to accelerated stability study and stored at 40 °C ± 2 °C. The 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 the previously described procedures to evaluate the stability of liquid solutions.

RESULTS

A series of alkyl alcohols were transformed into the corresponding ibuprofen esters in a good yield. The esterification reactions were followed by TLC characterization. A new single spot, with Rf different than ibuprofen Rf, was detected using UV lamp (Table 2).

Table 2: Rf values of Ibuprofen & synthesized alkyl esters

Compound	Rf Value
Ibuprofen	0.5
Methyl- ibuprofen	0.56
Ethyl- ibuprofen	0.63
Propyl- ibuprofen	0.69
Butyl-ibuprofen	0.75
Pentyl-ibuprofen	0.875
Hexyl-ibuprofen	0.75

The molecular weights and the calculated Log p values of all synthesized esters of ibuprofen are shown in table 3. The calculation was performed using ChemDraw software.

Table 3: Molecular weight and partition coefficient data for ibuprofen and its derivatives

Compound	Molecular weight	Calc Log P Value
Ibuprofen	206.3	3.68
Methyl- ibuprofen	220.3	4.09
Ethyl- ibuprofen	234.3	4.61
Propyl- ibuprofen	248.4	5.14
Butyl-ibuprofen	262.4	5.67
Pentyl-ibuprofen	276.4	6.20
Hexyl-ibuprofen	290.5	6.73

The alkyl ester products were purified using column chromatography yielding transparent oils. All the produced esters have FTIR spectra that are different from the original FTIR spectra of the ibuprofen and its corresponding alkyl alcohol. The FTIR of Butyl-ibuprofen oil which was chosen for the formulation was characterized by FTIR the results are shown and summarized in (table 4).

Table 4: FTIR characterization of Butyl-Ibuprofen

Product	FTIR
Ibuprofen	ν C=O stretch 1708
	ν OH stretch 2919
	ν OH bend 1418
Ibuprofen Butyl ester	ν C=O stretch 1732
	ν OH stretch -----
	ν OH bend -----

The stability study results of Ibuprofen & Ibuprofen butyl ester for the tested samples were within the accepted pharmacopeal specification as reported in table 5.

Table 5: Stability Studies of Ibuprofen & Butyl-Ibuprofen

% Assay	Temp	1 Month	2 Month	3 Months
Ibuprofen	25°C	99%	99%	98%
	40°C	98%	98%	98%
Butyl-Ibuprofen	25°C	99%	99%	99%
	40°C	99%	98%	99%

DISCUSSION

For the topical formulation we chose butyl form the synthesized esters because it has the best balance of lipophilicity- hydrophilicity which makes it a good candidate as transdermal delivery system as shown in table 3 generally as expected the lipophilicity of all the synthesized ester is greater than the ibuprofen free acid. The increased lipophilicity is indicated by an increased in the calculated log P values of the synthesized ester.

The signals of the FTIR spectra of the synthesized compounds indicate the success of the chemical synthesis of the butyl esters, the sharp band of the carbonyl group of the carboxylic acid of the free ibuprofen has shifted from 1708 to 1732 which confirm the formation of ester. Moreover, the wide band of the hydroxyl group of free ibuprofen has disappeared in the synthesized ester.

The problem with formulated ester is its susceptibility to hydrolysis. In our formulation we have taken this into consideration and the vehicle used in formulation was not aqueous. The stability results of both accelerated and in normal condition were within normal limits. The stability study results of Ibuprofen & Ibuprofen butyl ester for 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 Ibuprofen & Ibuprofen butyl ester was within the accepted pharmacopeal limits.

CONCLUSION AND DISCUSSION

Alkyl Ibuprofen esters were successfully synthesized using an acid catalyzed esterification reaction. Topical solutions for ibuprofen and their butyl esters were successfully formulated. All formulations were stable during three months of stability studies. Future studies should include 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 Frans diffusion cell.

CONFLICT OF INTERESTS

Declared None

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