Introduction

Ibuprofen, R,S-2-(4-isobutylphenyl)propionic acid, and ketoprofen, R,S-2-(3-Benzoylphenyl)propionic acid are two common traditional nonsteroidal anti-inflammatory drugs (NSAID’s) administered orally as anti-inflammatory agents, analgesics and antipyretics. They exert their action by inhibiting the COX-1 and COX-2 enzymes which mediate the formation of prostaglandin precursors and thus control pain, inflammation, and fever in the body. As oral preparations, absorption of ketoprofen is almost complete and that of ibuprofen is greater than 85%, making oral therapy very effective. A known adverse effect of this type of administration route, however, is gastrointestinal irritation and ulceration due to the local effects of prostaglandin synthesis suppression in the gastric mucosa as the drugs undergo absorption. Also, a number of patients are not good candidates for oral therapy due to age, disease state, or other factors. A potential drug delivery system that would overcome these problems is a topical preparation such as a gel. Based on the physiochemical and pharmacokinetic properties of these NSAID’s, transdermal absorption of ketoprofen and ibuprofen is possible, with ketoprofen expected to be the better absorbed agent due to more favorable properties. The purpose of this study is to assess the extent to which these drugs can be absorbed transdermally from a gel preparation and to analyze the impact of changes to the formulation will be evaluated.

The secondary purpose is to evaluate the rabbit as a useful animal model to test differences in formulation on the extent to which these drugs can be absorbed transdermally from a gel preparation and to analyze the impact of changes to the formulation will be evaluated.

Materials & Methods

Preparation of 1% Ketoprofen Lipoderm TDG

Pluronic was dissolved in propylene glycol and mixed well with the lipoderm base.

Preparation of Pluronic 127 NF 20% Solution

The aqueous phase, composed of a Pluronic 127 gel was made using the following formula:

- Sodium Acetate: 100 mg
- Isopropyl Alcohol: 100 µL

The aqueous phase, composed of a Pluronic 127 gel was made using the following formula (reference needed):

- Ketoprofen USP: 30 mg
- Distilled Water: 1 mL

Ketoprofen was dissolved in propylene glycol and mixed well with the lipoderm base.

Pluronic 127 (aqueous) solution

Lecithin (organic) solution

Ketoprofen USP

Distilled Water

Potassium Sorbate

Isopropyl Palmitate

Ketoprofen was dissolved in the lecithin solution before introducing the aqueous pluronic phase and mixing well to form a gel.

The second formulation used PCCA’s Lipiderm® base. The gel was made based on the following formula:

Preparation of 1% Ketoprofen PLO Gel

Ketoprofen USP

Lecithin (organic) solution

Ketoprofen was dissolved in propylene glycol and mixed well with the lipoderm base.

Discussion

The IACUC approved the study protocol. Four New Zealand White rabbits were housed in a normal 12 hour light/dark environment with water freely available and were fed 150g of Standard rabbit chow along with grass. To carry out this study, 99.5% was obtained from Acros Organics. HPLC grade acetonitrile (lot UM1113) was purchased from Spectrum. Xylenes (lot 14267) and HPLC grade methanol (lot 073512) were procured from Fisher Scientific. Four New Zealand white rabbits approximately 1.5 Kg each were obtained from Charles River.

Evaluation of Transdermal Absorption of Ketoprofen in a Rabbit Model

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Results

A standard curve using various levels of ketoprofen in acetonitrile gave linear results with a correlation coefficient of 0.999 and a retention time of ~5 minutes. Unfortunately we did not obtain baseline separation from an endogenous substance in rabbit plasma. Therefore, blank peak areas at 5 minutes were subtracted from peak areas of unknown and spiked plasma. Siked samples gave a linear relationship with values about 1/3 the peak area of the standard curve. The results for the four rabbits each treated with the same dose of ketoprofen in two different vehicles appear in the graph below.

Ketoprofen Levels in Rabbits

The levels are at the low end of the therapeutic range. The discontinuity at 1.5 hours with the gel was because of ketoprofen’s 3’s results. Future studies should first develop a better assay method that avoids the interfering peak in the plasma and examines a series of dose levels using the Lipoderm® base.