STABILITY STUDIES ON NAPROXEN CREAM

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Abstract

Naproxen, (S)-6-methoxy-α-methyl-2-napthanlenaeacetic acid, is a NSAID, that is available by both prescription and over-the-counter in US. Currently, only the tablet and suspension formulation of this preparation is available in US. In this manuscript, we have investigated the stability of naproxen cream with two proprietary bases at both room temperature and at 4 °C over a three month period, and find that both 5% and 20 % formulations are chemically stable for at least a period of two months under both of these storage conditions.

KEYWORDS: Naproxen, Cream, Stability

INTRODUCTION

Naproxen is a proprionic acid derivative, chemical name – (S)-6-methoxy-α-methyl-2-napthanlenaeacetic acid. It is currently available in US both as regular and delayed release tablets, as well in suspension formulation. Naproxen was ranked 169th based on sales of the "top 200 generics" listed in 2007 and there were over 2 million prescriptions for this drug written in 2007 [1] . Literature search on PubMed indicated that there are no reports on naproxen cream in the literature. In this communication, we report stability of naproxen over a three month period at both 4 °C and at room temperature [25 ° C] in two different naproxen formulations.

MATERIALS AND METHODS

Stability of the following two formulations of naproxen creams were studied in this investigation. 1) Naproxen 5% in PLO gel Mediflow™ cream and 2) Naproxen 20% in PLO gel Mediflow 30™ cream. The compositions are mentioned in Table 1. The preparation chemicals including Naproxen (Lot#69645/F), Ethoxy Diglycol (Lot#094204), PLO gel Mediflo™ (Lot #72329) and PLO gel Mediflo 30™ (Lot #73829) were supplied by the sponsor (Medisca INC., Plattsburgh, NY). The buffering reagents like 85% orthophosphoric acid (Lot#094204), potassium hydroxide (Lot#106388) were of analytical grade and were procured from Fisher Scientific (Pittsburgh, PA). The acetonitrile (Lot#PB003606ACN) was of HPLC grade and was procured from Pharmaco-AAPER (Brookefeild, CT). For making the preparations, appropriate amount of the Naproxen was weighed out and triturated to produce fine powder using mortar and pestle. Required amount of the EDG was then added to the fine powder and levigated to produce a homogeneous suspension. The PLO base was then added to the Naproxen suspension a high speed unguator (Cito Unguator 014, Zella-Mehlis, Germany).

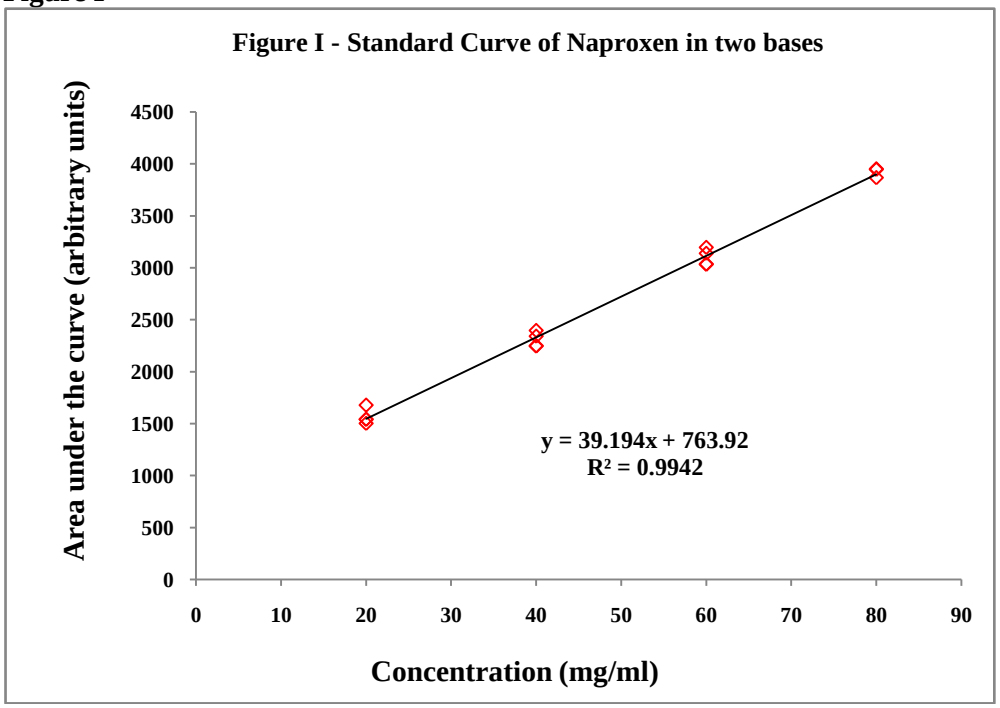
Primary Standard – One hundred milligram (0.1gram) of prepared naproxen (5 %) PLO gel Mediflow™ cream was weighed out with margin of plus or minus (0.0005 gram) and added to 50 ml phosphate buffer at pH 11.0 in a round bottom flask. For the naproxen (20 %) PLO gel Mediflow ™ 30 cream, the primary standard was made similarly with appropriate change in dilution (i.e. 200 mL Phosphate buffer was added instead of 50 mL). The contents were mixed well by vortexing for five minutes. Centrifugation is not necessary after stirring. The final concentration of naproxen in the supernatant was 100 µg/mL. The supernatant was called primary standard (PS).

Secondary standards were prepared by appropriate dilutions of the primary standard.

Chromatographic conditions - The stationary phase consisted of Zorbax Eclipse Plus Column (C8, 4.6x150 mm, 3.5 nm particle size, 95Å pore size, pH range 2-9, Agilent Technologies, Santa Clara, CA) and compatible Zorbax pre-column. The Mobile phase consisted of acetonitrile (75 %) and 0.02 M phosphate buffer at pH 11.0 (25%). The column temperature was maintained at 30 ^{o}C, the flow rate was 1.0 mL/min, and injection volume was 10 µL, while detection wavelength was 215 nm. The run time was six minutes. Under the described chromatographic conditions the retention time of naproxen is 1.2 minutes. For best results the column was conditioned by running the mobile phase at the described composition at a flow rate of 0.1 mL/min overnight.

Standard Curve -The vials marked with different secondary standards (10, 20, 30, 40, 50 µg/ml) filled appropriately (1.5ml) were injected in HPLC. The injections were made in a random order. Five sets of the secondary standards were prepared and injected to prepare the standard curve (figure 1). Standard curve has a correlation coefficient of 0.9942 and the area under the curve related to concentration by the following equation y = 39.194x + 763.92.

Figure I



RESULTS

The potency indicating stability data of the active ingredient Naproxen in the preparations are shown in the table 1. The potency is expressed in terms of mean of number of replicates (n, shown in the parenthesis). The standard deviation is shown as (± xx) for each data point. The data shows that more than 90% potency of Naproxen in both the formulations after incubation at room temperature (25ºC) for 90 days. The potency data for the refrigerated data shows similar results except for the 90 day sample for 5% Naproxen in PLO Medflow Primix Cream.

Table 1. Stability of 5 % and 20% Naproxen cream at 4 ^{o}C and 25 ^{o}C.

Stability as % labeled amount				
Time (days)	5 % Naproxen preparation		20% Naproxen preparation	
	4 ^{o}C	25 ^{o}C	4 ^{o}C	25 ^{o}C
0	101.43 ± 2.55 (4)	101.43 ± 2.55 (4)	99.97 ± 3.27 (4)	99.97 ± 3.27 (4)
30	99.18 ± 2.16 (4)	105.03 ± 3.78 (4)	99.48 ± 1.65 (4)	99.52 ± 2.92 (4)
60	99.00 ± 2.08 (4)	104.34 ± 2.25 (4)	96.69 ± 2.08 (4)	103.14 ± 2.60 (4)
90	86.60 ± 42.35 (4)	96.47 ± 3.21 (4)	94.51 ± 2.89 (4)	97.94 ± 5.20 (4)

DISCUSSION

NSAID's as a class of drugs is widely used by the US population [1]. Recent report on meta-analysis of various NSAID on cardiovascular risk indicated that while little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms, naproxen seemed least harmful [2] . Some of these class of drugs are available over-the-counter, and as several of them are ingredients in multiple combination products. Thus, in spite of their relative safety profile, there are many cases of emergency room visits and patient hospitalizations associated with the use of this drug class. Unintended and unwanted side effects of gastrointestinal bleeding and cardiovascular events have been reported with NSAID use [3] . As topical application of the product will have less toxicity, availability of topical formulations to relieve localized inflammation and pain, instead of systemic administration of the drug, will reduce the incidence of adverse effect and complications.

USP 795 clearly state that compounding is an integral part of pharmacy practice and is essential for the provision of good health care [4] . When a patient brings a prescription that is not commercially available, pharmacist is allowed by law to compound appropriate quantity of that preparation for that particular patient. When a preparation is compounded, it is the compounder's responsibility to ensure the stability of the product during its use by the patient, which will be reflected in the expiry date assigned to the product. In the absence of stability studies, USP recommends that water containing non-sterile formulations can be given a maximum expiry date of 14 days after formulation when stored at cold temperature between 2-8 $^{\circ}$C [4] . This study provides the scientific basis by which pharmacists preparing naproxen cream as stated in this manuscript could safely assign an expiry date of three months at room temperature, resulting in savings and convenience to both patient and pharmacist.

CONCLUSION

To our knowledge this is the first report on the stability of naproxen cream. Both 5% and 20% naproxen cream, formulated as suggested in this manuscript, is found to be stable for a period of three months at room temperature. Refrigeration is neither necessary nor helpful for preservation of stability of naproxen in these proprietary cream bases.

Acknowledgement

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