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STABILITY STUDIES ON DICLOFENAC CREAM

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ABSTRACT

Diclofenac is a non-selective COX inhibitor. In US, currently, it is available only in various tablet and solution formulations from commercial manufacturer. In this manuscript, we have investigated the stability of diclofenac sodium in cream preparations involving two proprietary bases , Poloxamar Lacithin Organogel (PLO) medflow premix ™ and Poloxamar Lacithin Organogel (PLO) medflow premix 30 ™, at both 4 °C and at 25 °C [room temperature] over a period of three months. During the three month period, less than 10% of the active ingredient degradation was observed at both 4 °C and 25 °C. Therefore, when diclofenac is compounded under these conditions, a three month expiry date will be appropriate. This communication will help compounding pharmacist put more appropriate end of use date on the product, thereby complying with USP 795 guidelines, decreasing drug wastage and saving time and money for both patients and the compounding pharmacist.

Keywords: Diclofenac; NSAID; Cream; Topical; Stability

1. Introduction

Diclofenac is a phenylacetic acid derivative. The chemical name is 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid. It is available in US only as a prescription medicine, and is currently available in following tablet forms – regular, XR, DR and ER, for oral use, as a solution for ophthalmic use, and more recently as 1% gel for use in osteoarthritis. Diclofenac was ranked 80th based on sales, in the "top 200 generics" list in 2007 and there were over 5 million prescriptions for this drug written in 2007 [1]. In this communication, we report stability of diclofenac sodium cream over a three month period.

2.Material And Methods

Primary Standard – One hundred milligram (0.1gram) of prepared diclofenac sodium (2%) PLO Medflow Premix™ (or diclofenac sodium (10%) PLO Medflow Premix™ 30) cream was weighed out with margin of plus or minus (0.0005 gram) and added to a 100 ml flat bottom flask. Twenty five (25) or 125 ml of deionized water (DIW) was added according to the preparation to get a concentration of 80 80 µg/mL. The contents were mixed well by vortexing for five minutes. The insoluble base components were eliminated by centrifugation at 20,000 rpm for 10 min. The final concentration of diclofenac sodium in the supernatant, called primary standard (PS), was 80 µg/mL.

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

Chromatographic conditions - The stationary phase consisted of Zorbax Eclipse Plus Column (C18, 4.6x150 mm, 3.5 µm 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 (70 %) and 0.02 M phosphate buffer at pH 8.2 (30%). The column temperature was maintained at 30 degrees centigrade, the flow rate was 1mL/min, and injection volume was 10 µL, while detection wavelength was 280 nm. The run time was ten minutes. Under the described chromatographic conditions the retention time of the Diclofenac sodium is 2.17 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.

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Standard Curve -The vials marked with different secondary standards (20, 40, 60, 80 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.
Linear regression analysis was performed to obtain the best fit for the standard curve. Linear regression analysis yielded a straight line with a correlation coefficient of 0.99 with both bases.

3. Result

Area under curve (arbitrary unit), following chromatography is a standard evaluation method in pharmacokinetics to determine the total amount of product present. In this case, area under the curve was used to determine the total amount of diclofenac sodium present in the preparation.
The Samples were incubated in container and closer system (cream/ointment tubes) to simulate the real life storage conditions. The cream/ointment tube is a tightly closed system. The relative humidity within the confined space of the tube is always expected to be 100%. The relative humidity in the laboratory/storage space is not representative of the conditions within the container and thus is not taken into account.

4. Discussion

NSAID's as a class of drug is widely used by the US population [1]. In spite of their relative safety profile, over and inappropriate use of these products leads to many cases of emergency room visits and patient hospitalizations which are associated with the use of this drug class. Unintended and unwanted side effects of GI bleeding and cardiovascular events have been reported with NSAID use [2]. 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. In this context, commercial preparation of Voltran 1% gel [containing diclofenac sodium] is available on prescription only and has been FDA approved for the treatment of osteoarthritis.
Massey *et al* [4] have compared the effectiveness of various NSAID in relieving short term topical pain and reported that topical diclofenac, ibuprofen, ketoprofen, and piroxicam had similar efficacy in relieving pain. In a report comparing different topical preparations of diclofenac, Kyuki et al [5] reported that cream formulation was more effective than ointment.
USP 795 clearly state that compounding is an integral part of pharmacy practice and is essential for the provision of good health care[3]. 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 beyond-the -use 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[3]. This study provides the scientific basis by which pharmacists preparing diclofenac cream, as stated in this manuscript could safely assign an expiry date of three months, resulting in savings and convenience to both patient and pharmacist.

Conclusion

In this communication we have studied the stability of diclofenac sodium cream as 2 and 10% formulation in a proprietary base. While we find that both these preparations are relatively stable over a period of three month duration, as less than 10% decrease in the total amount of activity occurs over the three month period, we will like to recommend that pharmacists can safely assign a three month expiry date for this preparation from the date of compounding.

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Table I: Stability as % control

Stability as % control				
Time (days)	**2% diclofenac sodium in PLO Medflow Premix Cream**		**10% diclofenac sodium in PLO Medflow Premix 30 Cream**	
	4 °C	**25 °C**	**4 °C**	**25 °C**
0	99.04 ± 3.08 (4)	99.04 ± 3.08 (4)	99.00 ± 2.52 (4)	99.00 ± 2.52 (4)
30	101.64 ± 1.64 (4)	103.36 ± 2.46 (5)	100.02 ±2.84 (5)	97.74 ± 4.84 (4)
60	97.74 ± 4.96 (4)	97.41 ± 4.97 (4)	97.28 ± 5.06 (4)	99.06 ± 4.25 (4)
90	92.87 ± 5.17 (4)	90.28 ± 2.96 (4)	94.62 ± 0.8994 (4)	93.88 ± 2.94 (4)

*The numbers in the parenthesis indicate the number of repetition of each sample (n).
§The potency is indicated as % of labeled amount is the mean of the number of samples. The coefficient of variation of each data point is expressed by (±).