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Original Article

Determination of Synthetic Precursors as Impurities in Diclofenac Sodium Raw Material

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Abstract

Impurities of drug substances may produce some side effects in patient. Diclofenac Na is a member of non-steroidal anti inflammatory drugs (NSAIDs) family, which is routinely used by patients for the treatment of rheumatoid arthritis and various pains. To develop a method for the determination of synthetic precursors which could be remained as impurities in raw drug materials, Na diclofenac powder was chosen in this study. High performance liquid chromatography was used to detect and separate diclofenac from its usual precursors. The chromatographic conditions were as follows: column; C18, mobile phase; methanol/water (55/45), flow rate; 1 ml/min, wavelength of detector; 254nm. The chromatogram obtained showed a reasonable separations of Na diclofenac and its precursors. This method of analysis is applicable in the final product inspection of Na diclofenac raw material.

Keywords: Diclofenac Na; Precursors; Impurities; HPLC.

Introduction

In general, pharmaceutical products used by patients may show side effects, sometimes even life threatening. The side effects of drugs may be produced by impurities of drug substances. These impurities could be originated from several sources, such as different synthetic pathways; photochemical, hydrolytic and heat decompositions(1-5). To develop a method for determining the synthetic precursors which could be remained as impurities in raw drug materials, Na diclofenac powder is a good candidate. In the literature instrumental analytical techniques (i.e. HPLC, GC) have been used to determine Na diclofenac and related compounds present in formulations and human plasma (6,7) but no special method for detection and separation of the drug from its precursors has been introduced. In this study various methods of synthesis of diclofenac sodium were at first considered (8-10); among them, the one which was the most probably an industrial method was selected and used. (10). HPLC was then used to detect and separate the precursors as possible impurities present in the diclofenac sodium raw material.

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Experimental

Chemical substances and solvents were from Merck Co. and of analytical grades. For HPLC, methanol (HPLC grade) and water (distilled and deionized) were used as mobile phase. HPLC instrument was from Waters Co. Model 501. The chromatographic conditions were as follows: column packing and dimensions, C_{18} µBondapak and 4.6×300 mm, 10 µm; eluent, methanol/ water (55: 45); flow rate, 1 ml/min; detection UV at 254 nm; sensitivity, 2; temperature, ambient.

The synthesis of diclofenac sodium was performed based on a previous study (10). For chromatographic purposes, each chemical

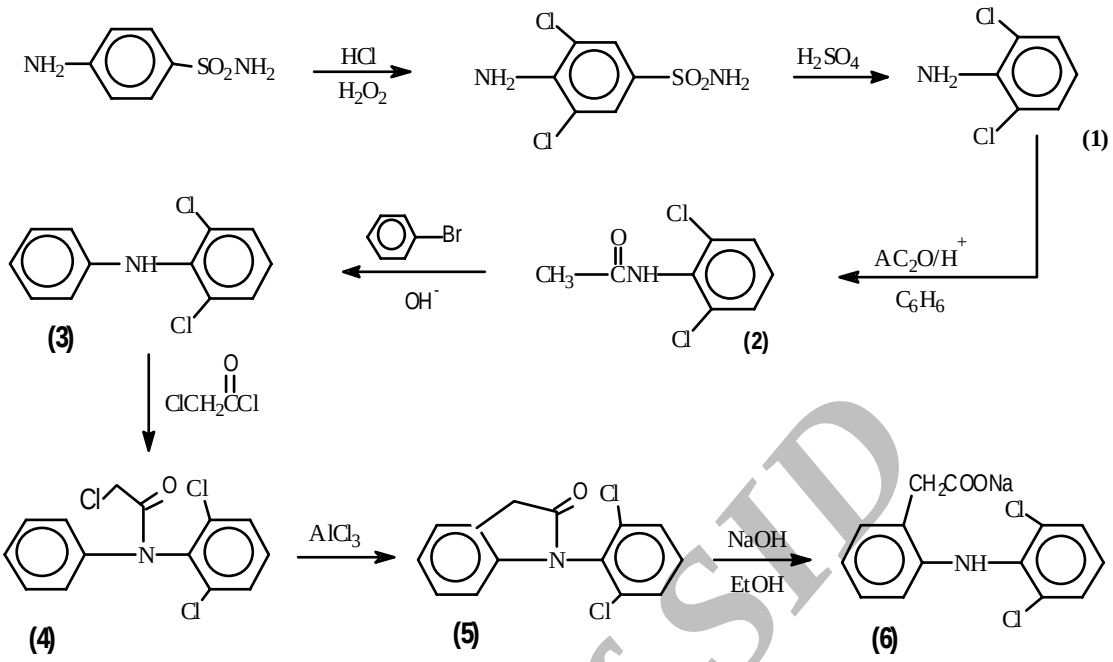

Figure 1. The sequence of synthesis of diclofenac Na

precursor and diclofenac sodium itself were individually prepared as a 2mg/lit concentration in methanol. 10µl of each sample was at first injected to the column. Then all the samples were mixed (5 µl of each) and 10µl of the mixture was taken and injected into the column.

Results and Discussion

The sequence of synthesis of diclofenac sodium is shown in scheme 1. There are 6 steps in this procedure. Steps 1 to 6 show the synthesis of 2,6-dichloroaniline, N-acetyl,2,6-dichloroaniline, N-phenyl-2,6-dichloroaniline, N-chloroacetyl-N-phenyl-2, 6-dichloroaniline, 1-(2,6-dichlorophenyl)-2-indolinons and Na diclofenace, respectively.

Based on the above procedure, five precursors were selected (designated as No. 1 to 5) in order to compare them with diclofenac sodium (No. 6) in analytical experiments.

Among the different methods of analysis, the reversed- phase HPLC method proved to be very reliable, accurate and easy to use for our experiments. The only problem regarding this method was finding suitable mobile phase. Using usual HPLC solvents, methanol/water mixture (55/45) was found to be a good choice as mobile phase. However, since diclofenac and its precursors could be ionized in an aqueous medium, adjusting pH towards acidic medium might be necessary. In our experiments in spite of the addition of acetic acid, peak tailing and double-top peaks were still noted. On the other hand, by employing PIC reagents, e.g.; sodium lauryl sulfate, an improvement in the

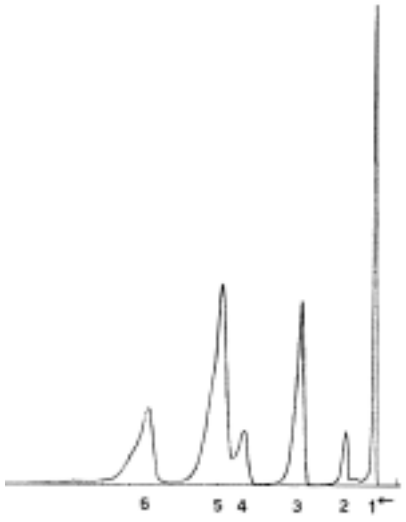

Figure 2. The HPLC chromatogram of diclofenac Na and its precursors.The eluted substances(peak, Rt (min)) : 1) diclofenac Na, 0.9; 2) N-acetyl-2,6-dichloroaniline,-1.8; 3) 2,6-dichloroaniline, 3.2; 4)1-(2,6-dichlorophenyl)-2-indolinone, 5.1; 5) N-chloroacetyl-N-phenyl-2,6-dichloroaniline, 5.9; 6) N-phenyl-2,6-dichloroaniline,8.3.

chromatogram of diclofenac separated from it's precursors was obtained as shown in figure 2.

In conclusion this method of analysis appears to be feasible for use in the inspection of manufactured pharmaceutical products.

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