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COMMUNICATION

Diclofenac Sodium: Oxidative Degradation in Solution and Solid State

Reynir Eyjolfsson

Eyrarholt 6, IS-220 Hafnarfjordur, Iceland

ABSTRACT

The formation of two oxidative degradates of diclofenac in solution and the solid state was demonstrated.
Key Words: *Diclofenac sodium; Stability; Tablets.*

INTRODUCTION

Although diclofenac (Fig. 1), mainly as sodium salt, has been used extensively and for a long time as a nonsteroidal anti-inflammatory drug (NSAID), information on its stability is scarce. Two decades ago, the cyclization of diclofenac to an indolinone derivative (a lactam) (Fig. 1) in acidic aqueous solutions was reported (1). Most of the experiments were carried out in 0.005–0.5 M hydrochloric acid at 60°C. In 1993, it was shown that this degradate could only be detected in diclofenac tablets that had been stored at severe conditions (90°C/55% relative humidity [RH]) for 20 days, but not in samples kept at 40°C/50% RH for 28 days or in commercial tablets (2). Recently, a paper was published stating the occurrence of two hydrolytic cleavage products of the indolinone derivative (i.e., oxindole and 2,6-dichlorophenol) (Fig. 1), in semiliquid formulations (gel ointments) of diclofenac that had been exposed to a high temperature (65°C) for prolonged periods of time (3).

This communication presents evidence for an oxidative degradation of diclofenac in solution and the solid state that resulted in the formation of two degradates.

MATERIALS AND METHODS

All raw materials used for tablet preparation were pharmacopeial (EP) quality, and all other materials were analytical grade. Granulation was carried out in an intensive mixer (Gral-25, Collette, Belgium), and tablet compression was in a rotary tableting machine (Manesty B3B, Manesty, UK). High-performance liquid chromatography (HPLC) analyses were performed according to the method described in the BP (mobile phase of phosphate buffer pH 2.5/methanol, 34/66, v/v) (4).

EXPERIMENTAL

Preparation of Tablets and Stability Trial

Diclofenac tablets, batch size 5.4 kg, were prepared by wet granulation, followed by drying, sizing, mixing with magnesium stearate and talc, and compaction to a target tablet mass of 270 mg and a strength of 75 mg (diclofenac sodium). The main excipients were hydroxypropyl methylcellulose (HPMC), lactose, microcrystalline cellulose, and povidone. The tablets (T1) were pack-

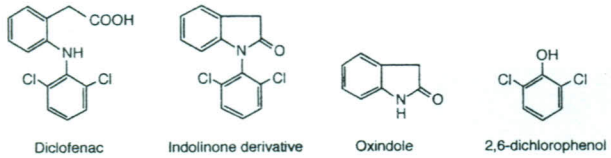

Figure 1. Structure of diclofenac and its known decomposition products.

aged into aluminum/PVdC (Al/PVdC [polyvinylidene chloride]) blisters, and a stability trial at 40°C/75% RH was conducted for 3 months.

Hydrolytic Trials Without Excipients

For hydrolytic trials without excipients, sample H1 was diclofenac-Na 45 mg plus 30 ml 0.33 M hydrochloric acid, which was heated at 100°C for 60 min, cooled to room temperature, and analyzed by HPLC. For sample H2, diclofenac-Na 45 mg plus 30 ml 0.33 M sodium hydroxide were heated at 100°C for 60 min, cooled to room temperature, and analyzed by HPLC. For sample H3, diclofenac-Na 100 mg, 1.0 ml water, and 0.1 M sodium hydroxide to pH 10 were heated at 100°C for 30 min, cooled to room temperature, and analyzed by HPLC.

Hydrolytic Trials with Excipients

For the hydrolytic trials with excipients, sample H4 was diclofenac-Na 100 mg, 100 mg HPMC, AND 1.0 ml water, which was heated at 40°C for 24 hr, cooled to room temperature, and analyzed by HPLC. For sample H5, diclofenac-Na 100 mg, 100 mg lactose, and 1.0 ml water were heated at 40°C for 24 hr, cooled to room temperature, and analyzed by HPLC. For sample H6, diclofenac-Na 100 mg, 100 mg povidone, and 1.0 ml water were heated at 40°C for 24 hr, cooled to room temperature, and analyzed by HPLC.

Oxidative Trials

For the oxidative trials, sample O1 was diclofenac-Na 0.2 mg, 2 mg ferric chloride ($FeCl_3$, 6 H_2O), and 10 ml 0.002 M hydrochloric acid, which was heated at 100°C for 25 min, cooled to room temperature, and analyzed by HPLC. For sample O2, diclofenac-Na 7.5 mg plus 10 ml mobile phase were stored in a 100-ml volumetric flask at room temperature in white light for 7 days and analyzed by HPLC. For sample O3, diclofenac-Na 7.5 mg, 10 mg sodium metabisulfite ($Na_2S_2O_5$), and 10 ml mobile phase were stored in a 100-ml volumetric flask at

Table 1

Degradative Experiments with Diclofenac Sodium, Indolinone Derivative, and Oxindole in Solution and Solid State

Sample	Temperature (°C)	Time	Results (HPLC)
T1 Tablets in Al/PVdC blisters	40/75% RH	3 months	Deg-1 0.11%; Deg-2 0.21%; see Fig. 2, A
H1 Dic-Na + 0.33 M HCHl	100	60 min	No peaks
H2 Dic-Na + 0.33 M NaOH	100	60 min	No peaks
H3 Dic-Na + H_2O, pH 10	100	30 min	No peaks
H4 Dic-Na + HPMC + H_2O	40	24 hr	No peaks
H5 Dic-Na + lactose + H_2O	40	24 hr	No peaks
H6 Dic-Na + povidone + H_2O	40	24 hr	No peaks
O1 Dic-Na + $FeCl_3$, pH 2.6	100	25 min	Deg-1 (large); Deg-2 (small); see Fig. 2, B
O2 Dic-Na + mobile phase + air + light	RT	7 days	Deg-1 (large); Deg-2 (small); similar to Fig. 2, B
O3 Dic-Na + mobile phase + $Na_2S_2O_5$ + air + light	RT	7 days	Deg-2 only
O4 Indolinone derivative + mobile phase + air + light	RT	7 days	No peaks
O5 Oxindole + mobile phase + air + light	RT	7 days	No peaks

Deg-1, degradate-1; Deg-2, degradate-2; Dic-Na, diclofenac sodium; RH, relative humidity; RT, room temperature. Percentages of degradates are relative to diclofenac.

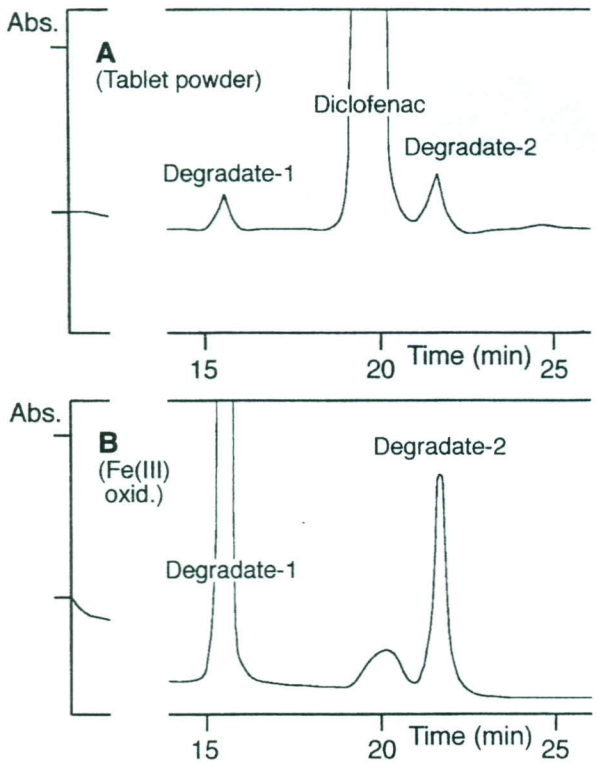

Figure 2. HPLC chromatograms of the two oxidative degradates of diclofenac.

room temperature in white light for 7 days and analyzed by HPLC. For sample O4, indolinone derivative 0.75 mg and 1.0 ml mobile phase were stored in a 10-ml volumetric flask at room temperature in white light for 7 days and analyzed by HPLC. For sample O5, oxindole 7.5 mg and 10 ml mobile phase were stored in a 100-ml volumetric flask at room temperature in white light for 7 days and analyzed by HPLC.

RESULTS

The results of the experiments are enumerated in Table 1 in terms of the two unknown diclofenac degradates detected in HPLC chromatograms and having $R_{t(D)}$ (relative to diclofenac) values of about 0.8 (degradate 1) and 1.1 (degradate 2) (Fig. 2).

DISCUSSION AND CONCLUSIONS

The two unknown degradates [$R_{t(D)}$ (relative to diclofenac) about 0.8 (degradate 1) and 1.1 (degradate 2), Fig. 2A] were first discovered in HPLC stability testing of diclofenac tablets (Table 1, T1). Their possible identity with the previously known degradation products of diclofenac (Fig. 1) could safely be ruled out since the known degradation products have much shorter retention times in the HPLC system used [the $R_{t(D)}$ values are about 0.2, 0.35, and 0.5 for oxindole, 2,6-dichlorophenol, and the indolinone derivative, respectively]. Several hydrolytic experiments performed on diclofenac sodium with and without the presence of tablet excipients (Table 1, H1–H6) did not furnish any evidence on the formation of the degradates in question. By contrast, oxidation of diclofenac sodium with iron (III) in a moderately acidic aqueous solution at 100°C (Table 1, O1) resulted in practically complete loss of the drug. Instead, the appearance of an intense peak corresponding to degradate 1 and another signal of low intensity conforming with degradate 2 was evident in the HPLC chromatogram of the reaction mixture (Fig. 2B). Both these peaks were also detected by HPLC in similar ratios in a solution of diclofenac sodium in the HPLC mobile phase on standing at room temperature for 7 days in the presence of white light and atmospheric oxygen (Table 1, O2). The presence of an antioxidant (sodium metabisulfite) in this solution prevented the formation of degradate 1, but had apparently little or no effect on degradate 2 (Table 1, O3). The known degradation products of diclofenac, the indolinone derivative and oxindole (Fig. 1), did not furnish either of the degradates on oxidation in solution with atmospheric oxygen (Table 1, O4 and O5). Therefore, it appears that these two degradates are formed by oxidative attack on the diclofenac molecule itself.

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