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On the Specific Diclofenac–Iron Cation Interaction for Selective Diclofenac Removal from a Water Solution

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Abstract: Diclofenac is one of the most common, commercially available, non-steroidal anti-inflammatory drugs (NSAIDs) in the world, with thousands of tons produced and consumed per year, which creates issues related to its presence in water bodies and the need for its removal from them. Diclofenac forms complexes with cations of each metal, which has inspired a study to check if the formation/precipitation of such complexes can be used for effective diclofenac removal from water solutions. It was found that iron salts, e.g., $FeCl_3$, can be used to remove diclofenac from a water solution in the form a of precipitated complex, provided that a high excess of iron salt was used. It has been observed that the diclofenac initial concentration of 5×10^{-4} M, as a result of $FeCl_3$ addition, after 48 h, decreased by two orders of magnitude. Salts of other metals were found less effective in reducing diclofenac concentration. The iron cation–diclofenac interaction was found to be specific, since the precipitation of other drugs by iron cations has not been observed. In order to quantitively analyze the diclofenac removal (precipitation) by iron and other metal cations, the HPLC/ESI-MS analyses were performed.

Keywords: diclofenac; iron complexes; precipitate; electrospray ionization; mass spectrometry; liquid chromatography

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1. Introduction

Diclofenac is one of the most common, commercially available, non-steroidal anti-inflammatory drugs (NSAIDs) in the world. As one of the drugs of which thousands of tons are produced/consumed per year, it creates issues related to its occurrence in the environment, waste water, and even in drinking water [1–5]. As a consequence, it creates a need to develop an effective method for diclofenac removal from water or an effective degradation method [6–8]. The most common removal methods seem to be membrane separation [3], bank filtration, provided that it is performed under the respective conditions [5] and adsorption methos [9]. Methods of diclofenac degradation, e.g., by photocatalytic processes, have also been widely developed [10].

Among the common NSAIDs, the metal cation complexes of diclofenac have probably been the most commonly studied, as they often show interesting biological activities, for example, anticancer activity, antileishmanial activity, radical scavenging properties, DNA binding ability, etc. [11–15]. Although the biological activities of the iron complexes of diclofenac have not been reported (to the best of our knowledge) and their anti-inflammatory activity is lower than that of the free drug [16,17], the complexes have attracted notable attention, namely, their spectroscopic and thermal properties have been studied in detail [18–21]. The unusual interaction of the Fe-diclofenac complex with cetirizine has been described in detail by Kenawi et al. [22]. Issa et al. have described an indirect atomic absorption spectrophotometric method based on diclofenac oxidation by Fe^{3+} under heating at 100 °C [23]. Iron cations may also affect (enhance or decrease) the process of diclofenac degradation [24–28]. It has also been demonstrated that the absorbers' functionalization with Fe^{3+} can be used for effective diclofenac removal from water [29,30].

Since diclofenac is probably able to form complexes with cations of each metal, it is reasonable to check if the formation/precipitation of the complexes can be used for diclofenac removal from a water solution. In this work, it is shown that the formation and precipitation of iron complexes with diclofenac can be used as an easy and effective way of diclofenac removal from a water solution. The iron cation–diclofenac interaction was found to be specific, since the analogical interaction of diclofenac with other metal cations and the interaction of iron cations with other drugs have not been observed.

2. Materials and Methods

Diclofenac (dic, in the form of its sodium salt) and all other drugs used (ibuprofen—ibf, naproxen—nap, ampicillin—amp, cefaclor—cfa), and inorganic salts ($FeCl_3$, $Fe(NO_3)_3$, $Fe_2(SO_4)_3$, $FeSO_4$, $CaCl_2$, $CoCl_2$, $CuCl_2$, $MnCl_2$, $ZnCl_2$), were obtained from Sigma-Aldrich (Poznań, Poland).

In order to show the selectivity of iron cations toward diclofenac, the following procedure was applied: a water solution containing a mixture of drugs (each with a concentration of 10^{-4} M) was prepared, and 0.1 mL of this solution was added to the 0.9 mL of methanol and directly infused into the mass spectrometer. Then, about 1 mg iron salt, e.g., $FeCl_3$, was added to 1 mL of the drug solution, which caused the solution to become turbid; after a few minutes, 0.1 mL of the solution was added to 0.9 mL of methanol and directly infused into the mass spectrometer. Direct infusion electrospray mass spectra (DI-ESIMS) were recorded on a Waters/Micromass (Manchester, UK) Q-tof Premier mass spectrometer (software MassLynx V4.1, Manchester, UK). The sample solutions were infused into the ESI source by a syringe pump at a flow rate of 5 mL/min. The electrospray voltage was 2.7 kV and the cone voltage was 30 V. The source temperature was 80 °C and the desolvation temperature was 250 °C. Nitrogen was used as the cone gas and desolvating gas at the flow rates of 0.8 and 13 L/min, respectively.

In order to quantitively analyze the diclofenac removal (precipitation) by iron and other metal cations, a solution containing diclofenac and an excess of an inorganic salt (1/6) was prepared and, after 48 h, the solutions were analyzed by HPLC/ESI-MS. Then, the HPLC/ESI-MS analyses were performed using a Waters model 2690 HPLC pump (Milford, MA, USA), and a Waters/Micromass ZQ2000 mass spectrometer (single quadrupole type instrument equipped with an electrospray ion source, Z-spray, Manchester, UK). The software used was MassLynx V3.5 (Manchester, UK). Using an autosampler, the sample solutions were injected onto the XTerra® MS C18 column (5 µm, 150 mm × 3 mm i.d.). The injection volume was 1 µL. The solutions were analyzed by using a linear gradient of CH_3CN-H_2O at a flow rate of 0.4 mL/min. The gradient started from 0% CH_3CN—95% H_2O, with 5% of a 10% solution of formic acid in water, reaching 95% CH_3CN after 8 min, and the latter concentration was maintained for 7 min. The ESI mass spectra were recorded in both the positive and negative ion mode, in the m/z range 100–1000. The negative ion mode was found to be more suitable (Figure S2, Supplementary Materials); therefore, the quantitative analysis was only performed in the negative ion mode. The nebulizing and desolvation gas was nitrogen at the flow rates of 100 and 300 L/h, respectively. The source temperature was 120 °C, and the desolvation temperature was 300 °C. The electrospray source potentials were as follows: capillary 3 kV, lens 0.5 V, extractor 4 V, and cone voltage 30 V. Each sample was run in triplicate, $R^2 = 0.97$, and the relative standard deviations were below 10%.

3. Results and Discussion

The DI-MS analysis of the solution containing the drug mixture clearly showed that diclofenac was selectively precipitated by iron cations. Four common carboxyl group-containing drugs were selected, namely ibuprofen—ibf, naproxen—nap, ampicillin—amp and cefaclor—cfa. Figure 1 shows the direct infusion mass spectrum of the drug solution and the spectrum obtained for this solution after $FeCl_3$ addition. Although only diclofenac and ampicillin were in the form of sodium salts, abundant $[M + Na]^+$ ions were observed

for all drugs. It is evident that the addition of $FeCl_3$ resulted in a substantial decrease in the diclofenac-assigned peaks, in contrast to the peaks corresponding to the other drugs (Figure 1). Analogous results were obtained for the other iron salts ($Fe(NO_3)_3$, $Fe_2(SO_4)_3$, $FeSO_4$). The abundant ion [amp + CH_3OH + H]$^+$ at m/z 372 is worth noting. It corresponds to the ampicillin methanolysis product, which has a higher ESI response than ampicillin [31], and the methanolysis process of β-lactams may be catalyzed by metal cations [32–34].

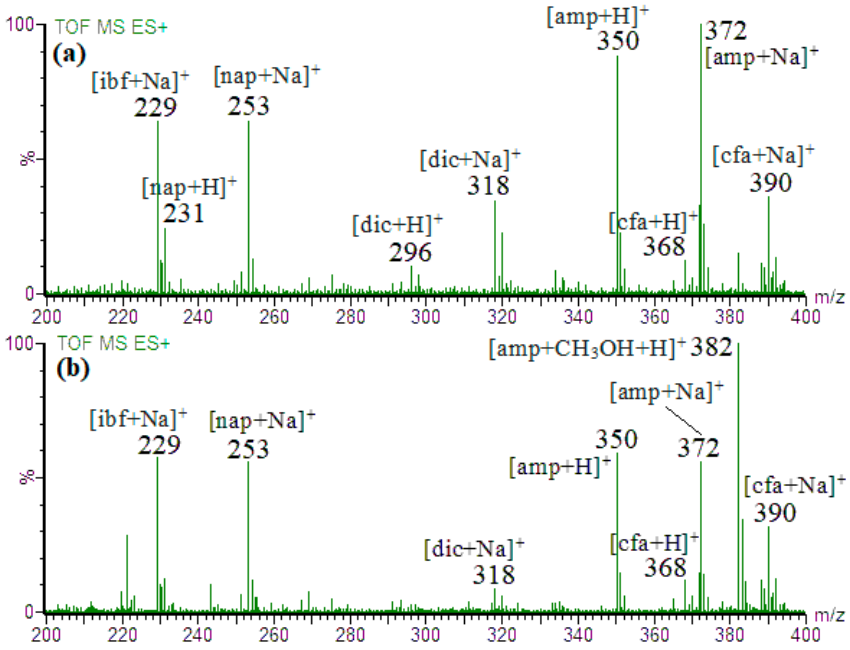

Figure 1. The direct infusion ESI mass spectrum obtained for the drug solution (**a**), and the direct infusion ESI mass spectrum obtained for this solution after adding $FeCl_3$ (**b**).

Diclofenac is probably able to form complexes with cations of each metal; however, it was found that a iron–diclofenac complex can be used for effective diclofenac removal (precipitation) from a water solution. Photographs of the vials containing selected obtained precipitates are shown in the Supplementary Materials (Figure S1).

Figure 2 presents the evidence for the decrease in diclofenac concentration, after 48 h, after addition of a 6/1 excess of the inorganic salt. The concentrations were analyzed by HPLC/ESI-MS; exemplary chromatograms are shown in the Supplementary Materials (Figures S2–S4). As shown in Figure 2, the most efficient diclofenac removal was observed after $FeCl_3$ addition, which means that the diclofenac–iron complex, under the conditions used, is the least soluble, in comparison to the complexes of other metal cations. The diclofenac initial concentration was 5×10^{-4} M, and after $FeCl_3$ addition, after 48 h, the diclofenac concentration was 5.5×10^{-6} M (which is the limit of detection of HPLC/ESI-MS(-) method used—Supplementary Materials, Figure S2). The other iron salts (both Fe^{III}/Fe^{II}) were also quite effective in removing diclofenac from the solution, although the counter ion slightly affected this process (it is reasonable that in the presence of nitrate or sulfate anions, the formed complexes are more soluble). Cr^{III} and Cu^{II} were found to be relatively effective metal cations, although less effective than Fe cations. It has to be also pointed out that effective diclofenac removal by iron salts does not occur at low pH values (e.g., pH = 2, Figure 2). It is reasonable that at low pH values, the protonation of diclofenac affects the formation of the diclofenac complex with iron cations.

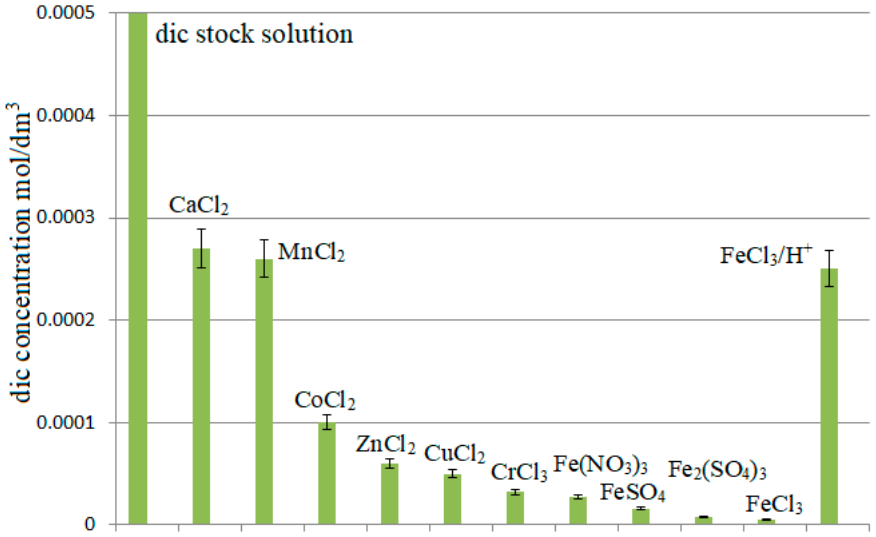

Figure 2. The decrease in diclofenac concentration, 48 h after the addition of inorganic salts.

It is plausible that the formed Fe^{III}-diclofenac complexes are of stoichiometry 1:3, and the FeII-diclofenac complexes are of stoichiometry 1:2 [17–20,22]. However, it was found that in order to attain effective diclofenac removal, a high excess of iron salts has to be used, as shown in Figure 3 (exemplary chromatograms are shown in the Supplementary Materials, Figure S5); namely, the iron salt/diclofenac ratio should be >5/1. It also indicates that the high ionic strength does not affect the diclofenac removal from the solution.

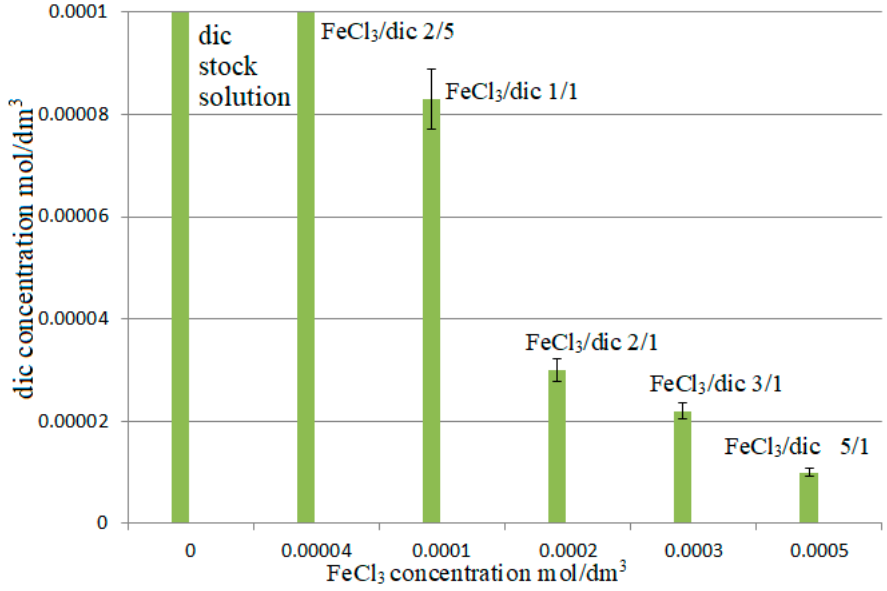

Figure 3. The decrease in diclofenac concentration, 48 h after the addition of iron salts.

4. Conclusions

Summing up, the formation/precipitation of diclofenac-$Fe^{III/II}$ complexes in a water solution was found to be specific; namely, the processes involving iron complexes with other drugs and diclofenac complexes with other metal cations are less favored than that of the diclofenac-$Fe^{III/II}$ complexes. Therefore, when the removal of diclofenac from a water solution is required, the iron salts can be used for this purpose. Although the diclofenac residue in the solution was approximately ~10^{-6} mol/dm^3, which may be regarded as not low enough, the advantage of the presented approach is its simplicity. The diclofenac remaining in the solution can be degraded by using well-established methods, e.g., by the

Fe(II)/peracetic acid process [26], electro-oxidation [35], or microbial transformation [36]. The use of iron salts for diclofenac removal may be also considered as an advantage, since iron salts are of a low acute toxicity and they are commonly present in the environment (iron is the fourth most abundant element on Earth). Therefore, the use of iron salts does not contribute to environmental pollution (https://archive.epa.gov/pesticides/reregistration/web/pdf/4058fact.pdf, accessed on 25 September 2024). Of course, the possible negative effect of iron salts on the environment and human health cannot be totally ignored, and the possible anthropogenic emission of iron salts, if possible, should be avoided.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/separations11100285/s1, Figure S1: Photos of the vials containing the selected obtained precipitates of diclofenac complexes with metal cations; Figure S2: Exemplary single ion chromatograms of diclofenac $[M\text{-}H]^-$ ion (m/z 294, top) and $[M + H]^+$ ion (m/z 296, top); Figure S3: Exemplary single ion chromatograms of diclofenac $[M\text{-}H]^-$ ion (m/z 294) obtained for the diclofenac stock solution (bottom) and for the solutions after inorganic salt addition; Figure S4: Exemplary single ion chromatograms of diclofenac $[M\text{-}H]^-$ ion (m/z 294) obtained for diclofenac solutions after iron salt addition; Figure S5: Exemplary single ion chromatograms of diclofenac $[M\text{-}H]^-$ ion (m/z 294) obtained for diclofenac stock solution (bottom) and for the solutions after iron salt addition.

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