New approaches to the synthesis of diclofenac choline

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ABSTRACT

The process described herein proceeds to obtaining diclofenac choline from choline bicarbonate and diclofenac acid in mild conditions, using non-toxic solvent, with the same impurity profile deriving from diclofenac particle as for diclofenac sodium EP. The substance is also substantially free from impurities deriving from choline and free from inorganic by-products, what means that the quality may be accepted for use as an active substance in medicine.

Keywords: Diclofenac choline, Anti-inflammatory agent, Oromucosal solution, Mouthwash solution

1. Introduction

Diclofenac as an active moiety of chemical name [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid belongs to the group of non-steroidal anti-inflammatory drugs (NSAID) and causes inhibition of prostaglandin synthesis.

Diclofenac is used to reduce pain and inflammation, and is administered mainly orally and topically, but also in a form for injection. Diclofenac acid shows very poor water solubility, what is the main problem in development of medicinal formulations of sufficient bioavailability. It causes that diclofenac is used in medicine mainly in the more soluble salt forms containing inorganic counterions as sodium and potassium.

Diclofenac was firstly synthesized by Sallmann and Pfister in 1973, but further improvements and shortening of the synthesis process using PdI₂ as the catalyst are known. New diclofenac derivatives of improved solubility are also described, as the salt of diclofenac with hydroxyethylpyrrolidine developed by Avogadri. Diclofenac epolamine for topical treatment was approved by the FDA in 2007.
Diclofenac acid itself is marketed as 0.75 mg/mL mouthwash (oromucosal solution), but to enhance its solubility in water, choline base i.e. choline hydroxide is added to the formulation, what causes in situ diclofenac choline salt formation, which solubility in water is 250 000 folds better than diclofenac acid⁶ and better than the solubility of sodium and potassium salts.

Diclofenac mouthwash is useful in administration for postoperative pain after periodontal surgery⁷⁻⁹ and shows a very good safety in the treatment⁸,¹⁰. This medicine showed positive results on pharyngodynia and odynophagia¹¹, in symptomatic relief in all types of aphthous ulceration¹². Also is effective in reducing postoperative periodontal pain¹³ and in the treatment of mucositis by radiotherapy.¹⁴

The disadvantage of choline used in the oromucosal formulation of diclofenac is need for using large amounts of ingredients capable of masking its taste and odour, as 0.5% (w/w) of acesulfame potassium and 35% (w/w) of sorbitol, and that is why tromethamine was proposed to enhance the solubility of diclofenac acid.¹⁵ Moreover choline base has a tendency for degradation resulting colour formation and this is the reason that formulations also need to be dyed.

Although the synthesis of diclofenac choline, which is really formed in situ in the oromucosal formulations, from diclofenac in the acid form in equimolar ratios with choline hydroxide was patented in 1990th, diclofenac choline salt (see Fig. 1) has not been marketed as an active substance until now.¹⁶

Fig. 1. Diclofenac choline

The obvious disadvantage of this method is the fact that choline hydroxide obtained in the common way is often contaminated with by products from synthesis, resulting from the competition between N- and O-ethoxylation, and molecules having a higher degree of ethoxylation are formed in the synthesis, as well as coloured impurities.¹⁷ Probably this is a reason that the title compound was not characterized in the patent as regards impurity profile, and even recrystallized may be obtained as a coloured (nearly white) solid with melting point of 178.8 – 179.7°C.

Twenty years after the above mentioned first patent, the other synthesis method from diclofenac acid and choline chloride in a presence of base (preferably sodium or potassium hydroxide) was patented.¹⁸ Diclofenac choline obtained according to this method was a white solid with the same melting point, what suggests that coloured impurities may not have influence on the melting temperature range. The purity of diclofenac choline was not described, although there are special requirements set for the reagents (choline chloride should be of purity at least 98% on anhydrous basis and diclofenac acid should has assay at least 99% on anhydrous basis). Moreover, sodium chloride or potassium chloride (depending on the method) was formed as a by-product, subsequently removed by filtration of the solution of diclofenac choline in ethanol (required content of the solvent – at least 95%), which is used as the solvent for reaction. The disadvantage of this process is that sodium chloride and potassium chloride are soluble in aqueous solutions and even small quantity of water in the environment causes that these substances are not fully removable. Moreover, sodium chloride and potassium chloride are soluble in ethanol slightly and very slightly respectively, so there is a possibility that these salts are present in the final substance. The conclusion is that chlorides may be present as impurities in
diclofenac choline obtained by the method described in EP2598475, as a result of dissolving this salts in ethanolic reaction mixture and subsequent distillation to dry residue without additional purification.

Even though diclofenac choline is not used as an active substance, it is of researchers interest. Better solubility of diclofenac choline as compared to diclofenac acid and already marketed salts allows the use high concentrations of this substance in water systems or semisolid forms. Probably due to this fact, the substance can act rapidly administered topically and has an acceptable permeation via the cornea.19

Also the antioxidant activity of diclofenac choline was recently investigated and the conclusion that the anti-inflammatory effects may be enhanced by its scavenging activity against the ABTS, the DPPH, and the hydroxyl radicals, was presented20, so it may be concluded that diclofenac choline is a good candidate for a future active substance. The antimicrobiological activity was also observed for other organic salts of diclofenac, for example when the substance was coupled with imidazolium cation.21

To summarize, two synthesis methods for obtaining diclofenac choline are known in art, but both suffer with obvious disadvantages as regards impurities potentially present, subsequently there is no evidence concerning the purity of the title substance.

The goal of this study was obtaining diclofenac choline of improved purity, especially substantially free from impurities from choline base, inorganic by-products and also stable during storage, which quality allows using it as an active substance.

2. Results and Discussion

Synthesis of diclofenac choline

Diclofenac choline was synthesized from equimolar amounts of diclofenac acid and choline bicarbonate 80% aqueous solution, in acetone as an inert solvent. The synthesis proceeded with a very high yield of 95%. There is no inorganic by-products formed in the reaction in comparison to the already known methods, what is the result that bicarbonates liberate only water and carbon dioxide.

The structure of the obtained product was confirmed by $^1$H NMR (see Fig. 2 and Table 1) and $^{13}$C NMR (see Fig. 3 and Table 2) techniques.

![Fig. 2. $^1$H NMR spectrum of diclofenac choline (D$_2$O; 500 MHz)](image)

![Fig. 3. $^{13}$C NMR spectrum of diclofenac choline (D$_2$O; 126 MHz)](image)
Table. 1. $^1$H NMR results for diclofenac choline

<table>
<thead>
<tr>
<th>Proton</th>
<th>Chemical shift, δ ppm</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>2.96</td>
<td>singlet 9.866 [9H]</td>
</tr>
<tr>
<td>H-2</td>
<td>3.25, 3.26, 3.27</td>
<td>triplet 2.174 [2H]</td>
</tr>
<tr>
<td>H-3</td>
<td>3.58</td>
<td>singlet 1.994 [2H]</td>
</tr>
<tr>
<td>H-8</td>
<td>3.88–3.91</td>
<td>multiplet 2.173 [2H]</td>
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<tr>
<td>H-9 + H-10</td>
<td>6.77–6.82</td>
<td>triplet 1.998 [1H]</td>
</tr>
<tr>
<td>H-15</td>
<td>6.69, 6.71, 6.73</td>
<td>triplet 1.000 [1H]</td>
</tr>
<tr>
<td>H-14</td>
<td>7.10, 7.12</td>
<td>doublet 1.996 [2H]</td>
</tr>
<tr>
<td>H-11</td>
<td>7.18, 7.18, 7.19, 7.20</td>
<td>doublet of doublets 1.006 [1H]</td>
</tr>
</tbody>
</table>

Table. 2. $^{13}$C NMR results for diclofenac choline

<table>
<thead>
<tr>
<th>Carbon</th>
<th>Chemical shift, δ ppm</th>
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<tbody>
<tr>
<td>C-5</td>
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<tr>
<td>C-1</td>
<td>56.5, 56.6, 56.6</td>
</tr>
<tr>
<td>C-3</td>
<td>58.3</td>
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<td>C-9</td>
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<td>C-6</td>
<td>145.4</td>
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<tr>
<td>C-4</td>
<td>182.5</td>
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</table>

Diclofenac choline obtained as above, packed in double LDPE foil of 0.1 mm thickness and LDPE drum, was stored in a climatic chamber in accelerated conditions (40°C and 75% RH) for a period of 12 months. The substance was stable, what prognoses that in long-term conditions it should be stable for at least 2 years.

Profile of impurities

The profile of impurities determined with HPLC method deriving from diclofenac particle, was the same as for diclofenac sodium active substance complying with European Pharmacopeia (EP) requirements, as the last was employed for obtaining diclofenac acid for synthesis. The above means that the content of impurities specified according to EP, i.e. impurity A (1- (2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one), impurity B (2-[(2,6-dichlorophenyl)amino]benzaldehyde), impurity C 2-[((2,6-dichlorophenyl)amino]phenyl)methanol), impurity D (2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid), impurity E (1,3-dihydro-2H-indol-2-one) were not more than 0.2% (w/w), and total impurities were not more than 0.5% (w/w).
The impurities deriving from choline particle were assessed by $^1$H NMR technique and the substance obtained with the new method was substantially free of (2-hydroxyethoxy)choline, which is the known impurity of choline base obtained industrially. To compare, diclofenac choline obtained as per patent EP0521393 from commercially available choline base, has shown the presence of (2-hydroxyethoxy)choline on $^1$H NMR spectrum, which characterises *inter alia* with proton signals: triplet of chemical shifts 3.31, 3.32, 3.25, triplet of chemical shifts 3.47, 3.48, 3.49 and triplet of chemical shifts 3.63, 3.64, 3.65. (see Fig. 4).

![Fig. 4. $^1$H NMR spectrum of diclofenac choline obtained from choline base (D$_2$O; 500 MHz)](image)

Z = signals of impurity; (2-hydroxyethoxy)choline

The amount of residual solvent acetone was determined by loss on drying with result 0.16% (w/w), what was below the acceptable limit set for this solvent class, i.e. 5000 ppm.

3. Conclusions

The synthesis of diclofenac choline from diclofenac acid and choline bicarbonate aqueous solution, in acetone as a solvent, was performed with a very good yield of 95%. The synthesis procedure was carried out in mild conditions, using acetone as non-toxic organic solvent, which is similar to the route of epolamine salt. The substance, in opposite to the substance obtained according to the already know process from choline base does not need further crystallization and in opposite to the synthesis from choline chloride does not need removing inorganic by-products by filtration and subsequent distillation of the filtrate. Summarizing, the product obtained according to new procedure is free from impurities derived from choline and also in-organic by-products.

The synthesis of diclofenac choline from diclofenac acid and choline bicarbonate aqueous solution seems to be the best among already described methods for obtaining substance of a quality required in medicine. As regards impurities derived from diclofenac acid, choline and residual solvents content, the obtained product without additional purification, should comply with the requirements for drug substances.

4. Experimental

4.1. Reagents and chemicals

4.1.1. Synthesis of diclofenac choline

Diclofenac acid was obtained in neutralization reaction from diclofenac sodium of quality according to European Pharmacopoeia purchased from Amoli Organics Private Ltd. Acetone was purchased from Sigma-Aldrich. pH indicator was purchased from MERCK.
4.1.2. Nuclear magnetic resonance (NMR) spectroscopy analysis

D₂O 99.8% D (containing d₄-TSP as the internal standard) was purchased from Armar chemicals.

4.1.3. HPLC method for relative substances

Phosphoric acid p.a., sodium dihydrogen phosphate p.a. and methanol p.a. were purchased from Sigma-Aldrich. Diclofenac impurity A CRS was purchased from LGC Standards.

4.2. Instrumentation and NMR conditions

4.2.1. Synthesis of diclofenac choline

Magnetic mixer Heidolph. Dryer.

4.2.2. ¹H and ¹³C nuclear magnetic resonance (NMR) spectroscopy analysis

Bruker Avance 500 operating at 500 MHz (¹H) and 126 MHz (¹³C).

4.2.3. HPLC procedure for relative substances

Liquid chromatograph Shimadzu 10A with UV detector.

4.3. Synthesis procedure

5.0 g of diclofenac acid was dissolved in 65 mL of acetone. Choline bicarbonate 80% aqueous solution in equimolar amount (2.96 mL) was dropped during 15 minutes. The reaction was carried out for 30 minutes in the temperature of 35 – 40°C, then pH of the mixture was checked with pH indicator (pH should be about 7.0). The resulting suspension was chilled for 12 hours. The product was filtered and washed with fresh acetone. White solid in the amount of 6.35 g was obtained (yield 95%). Loss on drying was tested in the temperature of 105°C and the determined value was 0.14%.

4.4. HPLC procedure for relative substances

The procedure applied for determination of relative substances was adapted from EP monograph for diclofenac sodium.

Column:
—size: l=0.25m,Ø=4.6mm
—stationary phase: end-capped octylsilyl silica gel for chromatography R (5µm)

Mobile phase: mix 34 volumes of a solution containing 0.5 g/L of phosphoric acid and 0.8 g/L of sodium dihydrogen phosphate, adjusted to pH 2.5 with phosphoric acid, and 66 volumes of methanol.

Flow rate:1mL/min

Detection: spectrophotometer at 254 nm

Injection: 20 µL
References