



Research article

Preparation of diclofenac epolamine on a 100 g batch scale

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ABSTRACT

Diclofenac epolamine offers distinct advantages in solubility and permeability over other diclofenac salts, making it an excellent candidate for formulating transdermal patches or gels. Despite these benefits, existing published methods for preparing this ingredient remain hindered by several limitations. This article introduces a method for preparing diclofenac epolamine, achieving exceptional yield and purity, and utilizing commercially available, cost-effective diclofenac sodium as the starting material. The procedure employs three straightforward stages: acidification, salt formation, and purification, delivering an overall yield of 79.7% on a 100 g batch scale. The content of the resulting product ranges from 99.9% to 100.3%, as verified by high-performance liquid chromatography (HPLC). Structural confirmation of the synthesized compounds was established through a suite of spectroscopic techniques, including ¹H-NMR, ¹³C-NMR, mass spectrometry (MS), Fourier-transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD). This route demonstrates significant potential for industrial-scale production of diclofenac epolamine, providing a reliable source of raw material for topical formulations.

INTRODUCTION

Diclofenac, a derivative of phenylacetic acid that belongs to the NSAID group, is used

for acute pain treatment [1]. Due to its poor solubility, salts of diclofenac are used in preparations to address this problem [2, 3].

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Among diclofenac salts that have been studied, diclofenac epolamine offers a greater solubility (199.35 mM) compared to other salts, being two times greater than the solubility of diclofenac sodium (82.08 mM) and five times greater than that of diclofenac potassium (40.17 mM) [4]. In addition to significantly improving the solubility, diclofenac epolamine also increases the drug's lipophilicity and the permeability through the stratum corneum and the epidermis more than other salt types [5]. Given these advantages, this compound has been studied and applied in the preparation of patches or gels, employed to reduce inflammation, pain, and swelling in the joints [6], [7].

In previously reported literature, diclofenac epolamine was chiefly synthesized from diclofenac or 1-(2,6-dichlorophenyl)-2-indoline [8-10]. According to the work of Antonio Z. et al., one of the main advantages is that the title compound was produced from diclofenac only through a single reaction [8]. Despite this, diclofenac is not a readily available material on the market in large quantities [9], and neither the synthesis yield nor the purity of diclofenac epolamine was published. In addition, *n*-hexane was used for the purification, which belongs to solvent class 2 (should be limited in pharmaceutical products because of its inherent toxicity) [11]. The preparation detailed in the publication of Fini A. et al. also starts with diclofenac, achieving a product with high purity (> 99%). However, besides the aforementioned issue with obtaining diclofenac, the overall yield of the procedure was also not mentioned [10]. In 2010, Avogadri A. et al. published a synthetic procedure of diclofenac epolamine

from 1-(2,6-dichlorophenyl)-2-indoline, comprising three reactions with the latter two conducted in a "one-pot" reaction [9]. This process poses a risk of impurities due to the application of heat, yet both the melting point and the purity of the product were revealed.

Given that previous publications still have weaknesses and no study has been conducted in Vietnam on producing diclofenac epolamine, research on the preparation of the title compound is essential for the formation of patches and gels. In this paper, we report a preparation method on a 100 g batch scale for diclofenac epolamine that is convenient, simple, does not require heat, and has significant potential for scale-up synthesis.

MATERIALS AND METHODS

Diclofenac sodium 99.5% (Henan, China); epolamine 98.4% (Vietnam); diclofenac epolamine reference standard 99.9%, batch number D7021001 (Syntech Chem & Pharm, Taiwan); acetone 99.7%, diethyl ether 99.5%, methyl *tert*-butyl ether 99.5%, acetonitrile, methanol, ethanol 96%, hydrochloric acid 36% - 38%, *n*-hexane 95.0%, isopropyl alcohol 99.7% (Samchun, Korea); deionized water; absolute ethanol 99.7%; sulfuric acid 98% (Shanghai, China); ethyl acetate 99.5% (Samchun, Korea).

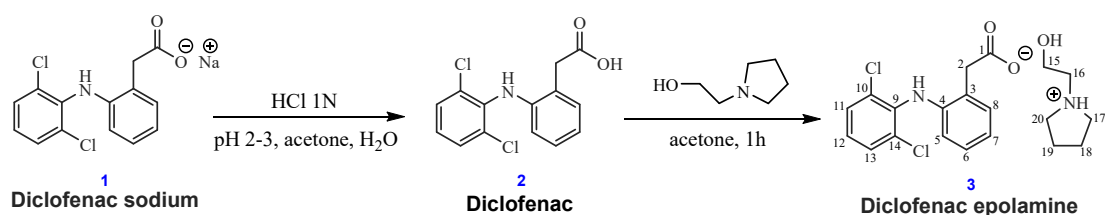
Methods

Synthesis:

Diclofenac epolamine was prepared through three stages (Scheme 1): i) Acidification. ii) Salt formation. iii) Purification

The reaction conditions were surveyed and modified from the related references [8-10].

Melting point measurement was applied for the preliminary purity evaluation, conducted on EZ-Melt SRS (USA) apparatus. The structure of diclofenac epolamine was



Scheme 1. Proposed route for preparing diclofenac epolamine

determined by spectroscopic data, including FTIR (Shimadzu spectrometer, Japan), ESI-MS (LC-MS/MS detector DAD, Shimadzu, Japan), HR-MS (Q Exactive Thermo Scientific - Resolution 35000, USA), ^1H - and ^{13}C -NMR (Bruker AV-500, USA), and XRD (Bruker AXS diffractometer, Germany).

Assay:

The content of the main compound was assessed using HPLC/DAD equipment (Agilent 1260). Chromatographic conditions: Column: Apollo C8 (250 × 4.6 mm; 5 μm), mobile phase: a phosphate buffer (pH 2.5) - methanol (34:66; v/v), flow rate: 1 mL/min, Injection volume: 20 μL, detector: UV ($\lambda = 254$ nm), temperature: 25°C, sample concentration: 50 μg/mL, diluent: mobile phase.

RESULTS AND DISCUSSIONS

RESULTS

Surveys for preparing diclofenac on a 1 g scale

Our primary idea for preparing diclofenac involves dissolving diclofenac sodium in a solvent selected for its ability to precipitate diclofenac upon acidification with 1 N HCl. To identify the most suitable solvent, a series of experiments were carried out, evaluating solvents based on the yield of the product and the volume of solvent utilized. The results, as reported in Table 1, indicated that a mixture of acetone and water in a 1:1 ratio provided the optimal conditions, meeting all the requirements. Additionally, the optimal pH

range for the synthesis was determined to be 2 - 3, as detailed in Table 2.

Table 1. The effect of solvent on its volume and reaction yield

Solvent	Ratio	Volume (mL)	Product mass (g)	Yield (%)
H ₂ O	-	500	0.81	87.0
Ethanol 96%: H ₂ O	1 : 1	200	0.87	93.5
Methanol : H ₂ O	1 : 1	65	0.76	81.6
Acetone : H ₂ O	1 : 1	15	0.91	97.8

Table 2. The effect of pH on reaction yield*

pH	Product mass (g)	Yield (%)
1.0	0.90	96.7
2.0	0.91	97.8
3.0	0.91	97.8
4.0	0.85	88.1

* Solvent: acetone : H₂O (1:1)

Preparation of diclofenac on a 100 g batch scale

In a 1000 mL beaker, 107.00 g of diclofenac sodium (337.48 mmol; 1 equiv.) was dissolved in 600 mL of an acetone-water (1:1) mixture. Then, 3.00 g of activated carbon was added to this mixture and stirred for 15 minutes at 50°C. The carbon residue was removed after filtration. After that, 1 N hydrochloric acid was added dropwise to the solution until pH reached 2-3. The precipitate was collected by vacuum filtration and washed with deionized water to eliminate the residual part of hydrochloric acid. Finally, the solid was dried at 70°C for 4 hours to obtain

product **2**. The procedure was conducted in three batches, achieving an average yield of 97.70 g (97.7%) of white solid, with m. p.: 170.3 - 172.8°C. **ESI-MS** (m/z): Calculated for $C_{14}H_{11}Cl_2NO_2$: 296.02 ($[M+H]^+$, ^{35}Cl), 298.02 ($[M+H]^+$, ^{37}Cl), found: 296.10, 298.10. **FTIR** (KBr) ν_{max} (cm^{-1}): 3322 (O-H), 1689 (C=O). **1H -NMR** (500 MHz, DMSO- d_6) δ (ppm): 12.70 (1H, s.br, OH); 7.53 (2H, dd, $J_1 = 1, J_2 = 8$ Hz, H-11, H-13); 7.24 - 7.17 (3H, m, NH, H-8, H-12); 7.07 (1H, t, $J = 7.5$ Hz, H-6); 6.87 (1H, t, $J = 7.25$ Hz, H-7); 6.29 (1H, d, $J = 8$ Hz, H-5); 3.70 (2H, s, H-2). **^{13}C -NMR** (125 MHz, DMSO- d_6), δ (ppm): 173.8 (C-1); 143.1 (C-9); 137.6 (C-4); 131.4 (C-10); 130.5 (C-3, C-14); 129.7 (C-11, C-13); 128.0 (C-8); 126.1 (C-6); 124.4 (C-12); 121.3 (C-7); 116.4 (C-5); 38.2 (C-2).

Surveys for preparing diclofenac epolamine on a 1 g scale

Regarding the process detailed in the work

of Antonio Z. et al. [8], diclofenac epolamine was formed by the reaction between diclofenac and epolamine in acetone before using *n*-hexane for precipitating the product. Initial surveys for reaction solvent confirmed that acetone was still the most appropriate choice, as it afforded the highest yield with minimal volume, as shown in Table 3. On the other hand, given that *n*-hexane is a class 2 solvent according to ICH guidelines [11], we assessed class 3 alternatives, namely diethyl ether and methyl *tert*-butyl ether, for less toxicity. The results showed a slight difference among the yields achieved with all the tested solvents (Table 4); however, diethyl ether offered the most favorable melting range for the final compound and proved more cost-effective than methyl *tert*-butyl ether. Therefore, diethyl ether was chosen for precipitating diclofenac epolamine in the process.

Table 3. Survey for the reaction solvent

Solvent	Volume (mL)	Product mass (g)	Yield (%)	M.p. (°C)
Ethanol	50	1.23	88.6	81.1 - 87.0
Methanol	100	1.12	80.7	73.8 - 79.1
Acetone	20	1.26	90.7	69.3 - 72.0
Ethyl acetate	80	0.70	50.4	100.0 - 103.0
Acetonitrile	80	1.09	78.5	71.0 - 72.3
Isopropanol	200	1.22	87.9	70.0 - 72.6
Diethyl ether*	30	1.24	89.2	71.5 - 72.4
Methyl <i>tert</i> -butyl ether*	50	1.19	85.7	91.0 - 99.0

* Used for both reaction and precipitation.

Table 4. Survey for the precipitation solvent

Solvent	Product mass (g)	Yield (%)	Appearance	M.p. (°C)
<i>n</i> -Hexane	1.20	86.4	Yellow and clumped solid	70.1 - 72.8
Diethyl ether	1.19	85.7	Light yellow and fine solid	70.0 - 72.5
Methyl <i>tert</i> -butyl ether	1.18	85.0	Light yellow and fine solid	71.8 - 76.0

Table 5. Survey for the crystallization solvent

Solvent	Volume (mL)	Product mass (g)	Yield (%)	Appearance	M.p. (°C)
Ethyl acetate	70	0.86	86.0	White and fine crystal	101.5 - 103.0
Absolute ethanol	15	0.44	44.0	White and fine crystal	70.2 - 74.3
Acetone	20	0.77	77.0	White and needle-shaped crystal	70.5 - 72.4
Acetone + ethyl acetate (1:1)	15	0.89	89.0	White and needle-shaped crystal	101.2 - 102.3

Surveys for the purification of diclofenac epolamine in a batch of 1 g

The final product was isolated via crystallization of the crude solid collected after the reaction. As indicated in Table 5, solvent screening identified a 1:1 mixture of acetone and ethyl acetate as the optimal crystallization solvent, since it yielded crystals with the desired melting range using minimal volume compared with other tested conditions.

Preparation of diclofenac epolamine on a 100 g batch scale

In a 2000 mL single-neck round-bottom flask, 72.00 g of diclofenac [2] (243.12 mmol, 1 equiv.) was dissolved in 700 mL of acetone. Then, 28.5 mL of epolamine (243.12 mmol, 1 equiv.) was dropwise added and stirred at room temperature for 1 h. After that, the solvent was removed by evaporation at 40°C until constant volume. Added to this mixture is 100 mL of diethyl ether; the precipitate was formed after minutes of stirring. It then was filtered, washed with diethyl ether, and dried at 40°C for 4 h to obtain a yellow solid. This procedure was conducted in three batches, achieving an average outcome of 91.86 g (91.7% yield) of light yellow solid, M.p. 70.6 - 72.1°C.

Purification: In a 1000 mL glass beaker, diclofenac epolamine [3] (100.00 g, 243.3

mmol, 1 equiv.) was dissolved in 600 mL of a mixture of acetone and ethyl acetate (1:1). Then, 3.00 g of activated carbon was added and stirred for 15 min at 50°C in a thermostatic bath, after which carbon residue was removed by filtration. The filtrate was transferred into a 2000 mL single-neck round-bottom flask. The solvent was removed by evaporation at 40°C until the mixture's volume reached around 100 mL to obtain the crystal. Subsequently, the crystal was filtered, washed with cooled acetone, and dried at 40°C for 4 h to obtain a white solid. This procedure was conducted in three batches, achieving an average result of 89.78 g (89.0% yield), with M.p.: 100.2 - 102.6°C. The content of diclofenac epolamine in three batches ranged from 99.9% to 100.3%. **HR-MS** (*m/z*): Calculated for C₂₀H₂₄C₁₂N₂O₃: 296.0245 ([M-epolamine+H]⁺, ³⁵Cl), 298.0216 ([M-epolamine+H]⁺, ³⁷Cl), 116.1075 [M-diclofenac+H]⁺; found: 296.0234, 298.0204, and 116.1071. **FTIR** (KBr) ν_{\max} (cm⁻¹): 3240 (OH); 2723 (NH⁺); 1575 (C=O); 1195, 1278 (C-N); 777, 739 (C-Cl). **¹H-NMR** (600 MHz, DMSO-*d*₆) δ (ppm): 8.84 (1H, s, N-H); 8.23 (1H, s.br, NH⁺); 7.48 (2H, d, *J* = 7.8 Hz, H-11, H-13); 7.15 (1H, dd, *J*₁ = 1.2 Hz, *J*₂ = 7.2 Hz, H-8); 7.12 (1H, t, *J*₁ = 8.1 Hz, H-12); 7.01 (1H, td, *J*₁ = 1.2 Hz, *J*₂ = 7.2 Hz, H-6); 6.82 (1H, td,

$J_1 = 1.2$ Hz, $J_2 = 7.2$ Hz, H-7); 6.30 (1H, d, $J = 7.2$ Hz, H-5); 3.64 (2H, t, $J = 5.7$ Hz, H-15); 3.55 (2H, s, H-2); 3.01 (4H, br.s, H-17, H-20); 2.97 (2H, t, $J_1 = 5.4$ Hz, H-16); 1.80 - 1.78 (4H, m, H-18, H-19). $^{13}\text{C-NMR}$ (125 MHz, DMSO-*d*₆), δ (ppm): 176.4 (C-1); 143.4 (C-9); 138.1 (C-4); 130.9 (C-10); 129.6 (C-3, C-14); 129.5 (C-11, C-13); 127.3 (C-8); 127.0 (C-6); 125.0 (C-12); 120.9 (C-7); 116.3 (C-5); 57.9 (C-15); 57.3 (C-17, C-20); 53.7 (C-16); 42.5 (C-2); 23.2 (C-18, C-19). **XRD** 2θ ($^\circ$): 10.85, 18.57, 40.89.

DISCUSSION

Preparation of diclofenac from diclofenac sodium

Compared to the method reported in the work of Avogadri A. [9], our developed procedure comprises fewer steps, as an alternative approach was used for preparing diclofenac utilizing the distinction between the solubility of diclofenac sodium and diclofenac. Surveys were conducted to find an appropriate solvent that can dissolve diclofenac sodium but not diclofenac. A preliminary assessment was conducted on the use of water; however, it was found that this pathway required a considerable volume of water while yielding a moderate amount of the product. When using mixtures of solvent, the required amount for acetone and water (1:1) offered several advantages compared to other tested solvents. Specifically, the solvent volume was reduced more than 33 times

compared to water, more than 13 times compared to a 1:1 ethanol-water mixture, and by a factor of more than 4 compared to a 1:1 methanol-water mixture. This approach also achieved a reaction yield exceeding 97%, which is the highest among the solvents considered.

For structural determination, FTIR showed absorption bands that are characteristic of certain groups in diclofenac's structure, such as 3321 cm^{-1} and 1688 cm^{-1} for hydroxy (-OH) and carbonyl (C=O) groups in carboxylic acid, respectively. The positive MS indicated ion peaks at m/z 296.10 and 298.10, corresponding to the $[\text{M}+\text{H}]^+$ ions of diclofenac containing ^{35}Cl and ^{37}Cl , respectively. The appearance of these two signals is due to the natural isotopic distribution of chlorine (^{35}Cl and ^{37}Cl). The chemical shift signals, which are in the proton and ^{13}C carbon NMR spectra, totally fit with the proton and carbon number of diclofenac.

Preparation and purification of diclofenac epolamine

Among the solvents screened as reaction media, acetone was selected for its superior performance in terms of reaction efficiency, minimal volume requirement, cost-effectiveness, and low toxicity. In the precipitation step, the procedure reported by Antonio Z. employs *n*-hexane as the precipitation solvent, classified as a class 2 solvent under ICH guidelines, highlighting its restricted application in pharmaceutical

Table 6. Purification yield and product's content

Batch	Product mass (g)	Yield (%)	M.p. ($^\circ\text{C}$)	Assay (%)
1	89.98	89.7	100.2 - 102.1	99.9
2	90.13	89.2	101.5 - 102.3	100.1
3	89.25	88.2	101.1 - 102.6	100.3
Mean value	89.78	89.0	100.9 - 102.3	-

processes [11]. Accordingly, we evaluated alternative solvents and identified diethyl ether, a class 3 ICH solvent with lower toxicity, as a suitable replacement [11]. The crude salt preparation yielded 91.7% on a 100 g scale, exceeding the 83.0% reported by Antonio A. on a 15 g scale [8]. However, the use of diethyl ether as a solvent also presents certain limitations, as it is highly volatile and prone to oxidation upon exposure to air, leading to the formation of peroxides with a potential risk of explosion [12]. Therefore, in future studies, we will focus on exploring strategies to overcome these drawbacks.

Diclofenac epolamine exhibits polymorphism with different melting temperatures in distinct crystalline forms, such as anhydrous diclofenac epolamine melting at approximately 100 - 104°C, diclofenac epolamine monohydrate at 70 - 72°C, and diclofenac epolamine dihydrate at 60 - 62°C [3, 13]. Owing to its superior aqueous solubility compared to the hydrated forms, the anhydrous polymorph is preferred for pharmaceutical formulations [13, 14]. When purifying by precipitation according to the reference method [8], with diethyl ether as the precipitating solvent, the reaction yield is quite high; however, the melting temperature does not reach the desired value. An alternative purification approach was crystallization using solvents including acetone, absolute ethanol, and ethyl acetate. Crystallization from ethyl acetate provided an 86.0% yield and met the target melting range; however, the substantial solvent volume required for dissolution resulted in excessive waste and posed challenges for scale-up. Meanwhile, acetone or ethanol as recrystallization media led to diminished yields due to their high ability to dissolve

diclofenac epolamine. To address these limitations, an optimized protocol was developed utilizing a 1:1 (v/v) acetone - ethyl acetate mixture, which reduced the dissolution volume by approximately fivefold relative to ethyl acetate alone while preserving both yield and melting point specifications.

Characteristic absorption bands for diclofenac epolamine could be observed in the FTIR spectrum, such as 3240 cm^{-1} for the -OH group of epolamine, and 2723 cm^{-1} for the NH^+ . The positive HR-MS showed m/z peaks of 296.0234 and 298.0204 specified for the ions of $[\text{M-epolamine}+\text{H}]^+$ containing ^{35}Cl and ^{37}Cl , respectively, and an m/z peak of 116.1071 specified for the ion $[\text{M-diclofenac}+\text{H}]^+$. In the $^1\text{H-NMR}$ spectrum, nearly all proton signals appeared except for those of -OH due to the flexible hydrogen peaks, which can be blunt and broad. In addition, the $^1\text{H-NMR}$ spectrum did not show the proton signal of H_2O in the formula (the H_2O proton signal when measured in $\text{DMSO-}d_6$ solvent appears at 3.33 ppm [2]), further assuring that the diclofenac epolamine salt form was anhydrous. In the $^{13}\text{C-NMR}$ spectrum, all carbon signals were recorded and were consistent with the expected formula. These combined spectral data help to fully identify the structure of diclofenac epolamine.

CONCLUSION

In conclusion, diclofenac epolamine was successfully prepared on a scale of 100 g via our developed method, affording an overall yield of 79.7%. The product content determined by HPLC analysis ranged from 99.9% to 100.3%. This procedure represents the inaugural synthesis of diclofenac epolamine in Vietnam and offers multiple advantages, including the utilization of

readily available diclofenac sodium as the starting material, the simplicity of the acidification, the compliance of the final product's melting point with pharmaceutical standards, the high purification yield achieved using an ethyl acetate-acetone mixture, and the reduced toxicity by substituting diethyl ether for *n*-hexane. These results indicate a possible use in the large-scale production of this active pharmaceutical ingredient, with the goal of achieving pharmaceutical raw material self-

sufficiency in Vietnam for the preparation of patches and gels.

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CONFLICTS OF INTEREST

None.

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