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THE TECHNOLOGY BASIS OF DICLOFENAC SUBSTANCE PRODUCTION

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The basis of the production technology of the diclofenac substance, which consists of five main technological stages, is justified and proposed. The proposed technological aspects of diclofenac substance production allow obtaining the target product with a total yield of 61 %. Material calculations were carried out to obtain 1 ton of the final diclofenac substance. The numbers of necessary technological equipment are selected, and a basic technological scheme for the production of diclofenac is proposed.

Key words: 2,6-dichloroaniline; potassium 2-(2-iodophenyl)acetate; copper iodide; diclofenac; basics of technology; material calculations; technological calculations; thermal calculations; basic technological scheme.

Introduction

Diclofenac or 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid is a nonsteroidal anti-inflammatory agent that belongs to phenylacetic acid derivatives. The pharmacological activity of diclofenac consists of the inhibition of the enzyme cyclooxygenase, which leads to the inhibition of the biosynthesis of prostaglandins from arachidonic acid [1, 2]. Diclofenac is a non-selective COX inhibitor with total absorption and extensive metabolism. Like other nonsteroidal anti-inflammatory drugs, it is often used as first-line therapy for treating acute and chronic pain, as well as inflammatory processes of various etiologies [1, 2]. Previously, it was used to eliminate pain, mainly rheumatological. However, after conducting more detailed clinical studies, it began to be used in neurology, traumatology in the treatment of professional sports injuries, and the rehabilitation of inflammations of the musculoskeletal system [1, 2].The drug is successfully used in ophthalmology, gynecology, and stomatology. In addition, recent studies have shown that diclofenac can be used in complex therapy for the treatment of heart diseases and some types of oncology [3].

Diclofenac is quite available on the modern pharmaceutical market in various dosage forms with various routes of administration, in the form of various means of potassium or sodium salts [4]. Most often, diclofenac is presented on the world pharmaceutical market in the form of sodium salt, to a lesser extent in the form of potassium salt, diethylamine, and epolamine salts, and in some cases as an acid [5] (Fig. 1).

Diclofenac drugs are produced in the form of tablets and capsules, including those with delayed release, as well as suppositories [4]. It can also be administered by injection or eye drops [4]. The use of gels or patches with a high content of diclofenac salts is very convenient. Diclofenac gel (containing 3 % diclofenac) is used to treat actinic keratosis [4]. With the correct dosage, the drug is safe and used in pediatrics starting from six months. Medicinal products containing diclofenac are often associated with serious adverse dose-dependent effects on the gastrointestinal tract, cardiovascular system, and kidneys. Long-term use of diclofenac can cause stomach ulcers and bleeding [6]. Therefore, it is important to search for diclofenac derivatives that will avoid such unpleasant consequences. Synthetic approaches based on structural modification of the diclofenac molecule have been used to improve the safety profile of drugs [7, 8].

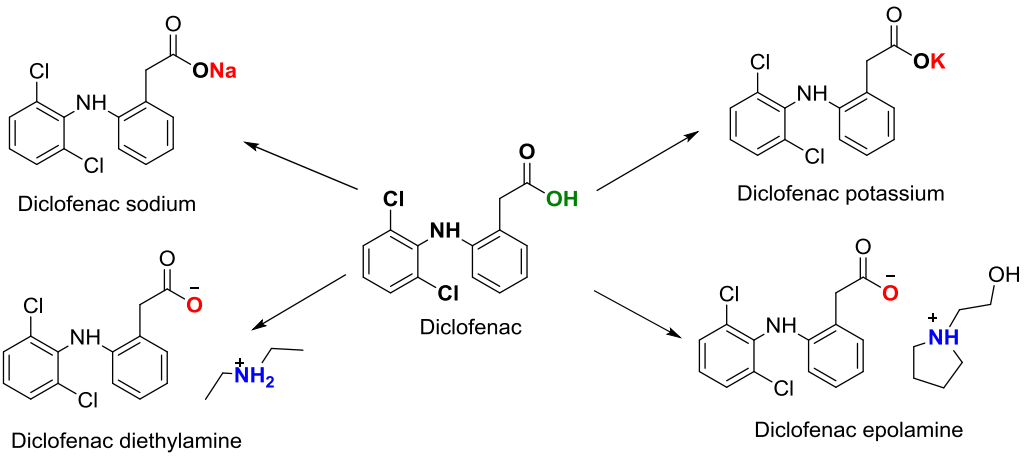

Fig. 1. Diclofenac salts, which are used as active pharmaceutical ingredients in medicinal products

The following fact confirms the relevance of the synthesis and production of diclofenac on an industrial scale in the modern world. The substance of diclofenac itself is convenient for obtaining its salts for the further production of drugs with anti-inflammatory and analgesic effects in various dosage forms. However, the main problem in obtaining the diclofenac substance is the low yield of the finished product, primarily up to 50 % [9]. It is known that the yield of the finished product directly depends on the conditions of the reaction. There are the solvent, the form and amount of the catalyst, and the temperature regime of the process [9].

In the literature, starting with the preparation of diclofenac in 1966, many different approaches to preparing this substance are presented [8]. There are five main directions for producing diclofenac, which are used by chemical and pharmaceutical companies worldwide, based on different starting reagents: cyclohexanone, *ortho*-iodophenylacetic acid, *ortho*-aminophenylacetic acid, isatin, and aniline [10]. However, each of these five production approaches have disadvantages, including the multi-stage process, low overall yield (30–50 %), the negative impact of production intermediates on the environment, complexity, and high cost of organizing the environmental protection process and waste disposal. Among the mentioned approaches, the method of production using aniline derivatives is considered by industrial manufacturers to be the most optimal from economic and environmental points of view [10].

A well-known industrial multistage method of obtaining diclofenac is the interaction of 2,6-dichloroaniline and 2-chlorobenzoic acid in the presence of sodium hydroxide and copper with subsequent transformations (Fig. 2) of the reaction products obtained (reduction, chlorination, substitution, and hydrolysis) with a yield of 32 % of the target product [11].

An improved laboratory method of obtaining diclofenac was proposed by Chinese authors [12], which includes the interaction of 2,6-dichloroaniline and potassium 2-(2-iodophenyl)acetate (Fig. 3), and the yield of 61 % of the target productis significantly affected by choice of catalyst, its cost and the conditions of the interactionitself.

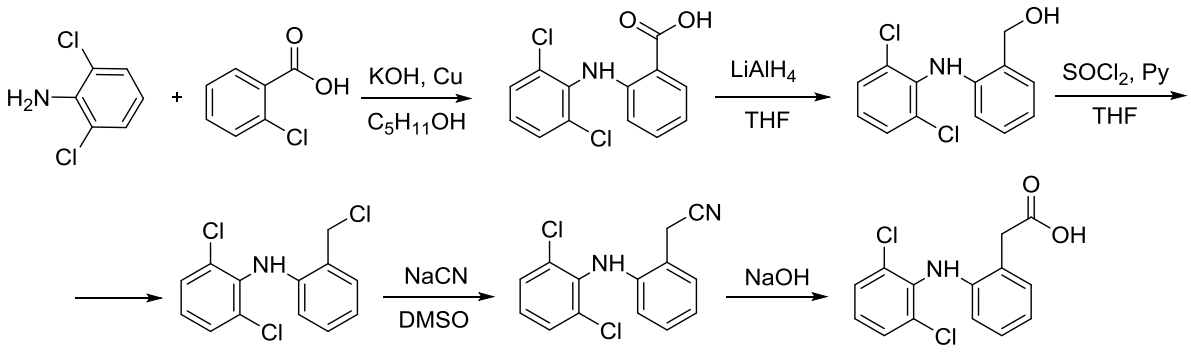

Fig. 2. General scheme for obtaining diclofenac from 2-chlorobenzoic acid and 2,6-dichloroaniline

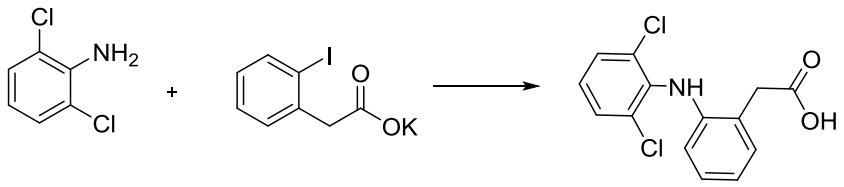

Fig. 3. General scheme of the improved method of obtaining diclofenac from 2,6-dichloroaniline and potassium 2-(2-iodophenyl)acetate

The purpose of this work is to scale up the laboratory method of obtaining diclofenac [12] to develop the basis of production with an increase in the total yield of the target product in the conditions of industrial production at chemical and pharmaceutical manufacturers. At the same time, it is necessary to carry out material, technological, and thermal calculations of such production. Also, a principle technological scheme for diclofenac substance production should be developed. The latter is convenient for obtaining its salts (Fig. 1), which are widely used as active pharmaceutical ingredients in various dosage forms.

Materials and research methods

A literature search and analysis on synthetic methods of obtaining diclofenac was carried out using the *SciFinder-n* database [13]. As a result, the influence of the catalyst, its amount, and the molar ratio of reagents on the yield of diclofenac was analyzed, and the method of laboratory synthesis was chosen [12]. Methods of systematization, analysis, and comparison of data from literary sources processed the obtained results. The following method was chosen from the source to scale up the laboratory synthesis of the diclofenac substance (Fig. 4) [12].

Potassium 2-(2-iodophenyl)acetate (0.150 mg, 0.50 mmol) was added to a mixture of 2,6-dichloroaniline (0.322 mg, 2.0 mmol), anhydrous potassium carbonate (0.345 mg, 2.5 mmol), copper iodide (0.191 mg, 1.0 mmol) in *N*-methylpyrrolidone (0.5 mL). The mixture was heated to 100 °C and stirred for 10 h. Then the mixture was cooled to room temperature, ethyl acetate (20 ml), water (10 ml), concentrated hydrochloric acid (0.6 ml), and activated carbon (2 g) were added, and stirring was continued for 1 h. The mixture was filtered to obtain two clear phases. The organic layer was collected and concentrated. The residue was purified by chromatography on silica gel to obtain the target product with a yield of 61 % [12].

The purity (%) of the reagents used in diclofenac synthesis is shown in Table 1. The equipment used in the laboratory method diclofenac preparation is presented in the article [12].

Diclofenac, white crystals, $C_{14}H_{11}Cl_2NO_2$, molar mass 296.15 g/mol, melting point 283–285 °C (from ether-petroleum ether), pKa 4.15, Log P 4.51, solubility: water, 2.37 mg/L, methanol, 35mg/mL, dimethyl sulfoxide < 2 mg/ml at 25 °C [14, 15]. Spectral data of diclofenac [12]: ^{1}H NMR (400 MHz, acetone-d_6) δ 7.47 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.21 (br, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 3.83 (s, 2H); ^{13}C NMR (100 MHz, acetone-d6) δ 173.2, 143.2, 138.1, 131.1, 129.7, 129.3, 127.9, 125.1, 124.9, 121.9, 117.7, 38.0.

Material, technological and thermal calculations were carried out following the calculation methodology given in the references [16–18].

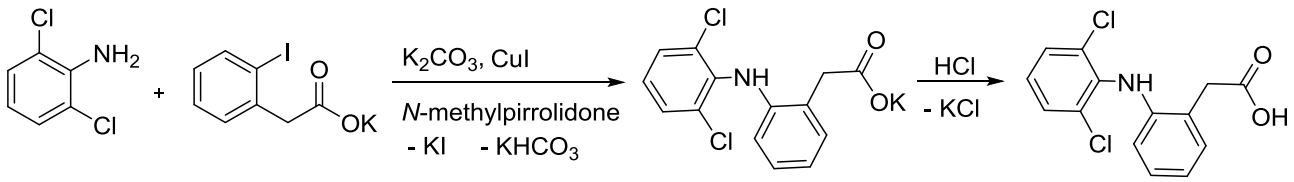

Fig. 4. Chemistry of the process of obtaining the diclofenac substance

Results and discussion

The following technological stages and yields were adopted for the design of scaling up the laboratory production of the diclofenac substance [12] in the industrial conditions of chemical and pharmaceutical production:

Stage 1. Production of potassium diclofenac, yield η_1 = 97 %;

Stage 2. Neutralization with hydrochloric acid and treatment with activated charcoal, yield η_2 = 100 %;

Stage 3. Filtration of the diclofenac reaction mixture, yield η_3 = 99 %;

Stage 4. Filtrate settling with separation of layers, yield η_4 = 89 %;

Stage 5. Precipitation of diclofenac, yield η_5 = 71 %.

The total yield of the proposed diclofenac production with the adopted stages is η_{tot} = 61 %.

For this production, material calculations were calculated [16–18], which at each stage made it possible to determine the consumption of the amount of raw materials to produce 1 ton of diclofenac substance. Diclofenac production capacity was assumed to be 350 tons/year. As a result of the material calculations, the amount norms for the industrial production of the diclofenac substance were determined (Table 1).

Technological equipment was selected based on technological calculations [16–18] (Table 2). As a result, the necessary quantity of each type of main and auxiliary equipment, its volume (length), the material from which it should be made, and the main dimensions were determined. The primary and auxiliary equipment to carry out the technological process must be made of stainless steel, for example, popular brands for the chemical and pharmaceutical industry, AISI 304 or 316. The main dimensions of the equipment were selected from the catalogs of the corresponding equipment [16]. The principle of combining their work in the technological process is shown in Fig. 5.

Table 1

Amount norms for the production of 1 ton of diclofenac substance at a capacity of 350 t/year

Substance name / purity %	Weight, kg		Volume*, m^3	Density*, kg/m^3
	Technical product	100 % Product		
2,6-Dichloroaniline / 99.0	3639.3251	3602.9319	2.8544	1275
Copper iodide / 99.5	2158.7301	2147.9365		
Potassium carbonate / 99.0	3899.2769	3860.2842		
2-(2-iodophenyl)acetate / 99.0	1695.3378	1661.4310	0.8994	1885
N-methylpyrrolidone/ 99.5	5803.7064	5774.6879	5.6511	1027
Hydrochloric acid / 36.0	1240.9873	1216.1675	0.6781	1830
Water	1130.2252		1.1302	1000
Activated charcoal	2260.4504			
Ethyl acetate / 99.5	2038.9263	2028.7316	2.2605	902

* *For liquid components.*

Table 2

Specification of primary and auxiliary equipment for the production of diclofenac substance

Name / symbol in Fig. 5	Volume, m^3	The main dimensions of the equipment, mm		Required number of apparatus, pcs.	Characteristics of the equipment
		Length	Height		
1	2	3	4	5	6
Reactor / R-1	6.0	1880	1800	3	shell, anchor stirrer, S = 13.4 m^2
Measuring tank / MT-1	2.0	2215	1000	1	for *N*-methylpyrrolidone
Storage tank / ST-1	8.0	3450	1600	1	
Measuring tank / MT-3	0.25	1105	500	1	for hydrochloric acid

Continuation of Table 2

1	2	3	4	5	6
Storage tank / ST-3	0.8	1325	800	1	
Condenser / Con-1			159	1	L_{tube} = 1.0 m, $L_{condenser}$ = 1.2 m (20*2/1)
Filter / F-1	1.6	1462	1210	1	F = 1.5 m^2
Collector / Col-1	16.0	4430	2000	1	for the filtrate
Reactor / R-2	4.0	1273,5	1800	2	shell, anchor stirrer, S = 10.6 m^2
Condenser / Con-2			273	1	L_{tube} = 1.50 m, $L_{condenser}$ = 1.85 m (20*2/1)
Storage tank / ST-2	3.20	2430	1200	1	for ethyl acetate
Measuring tank / MT-2	0.8	1725	800	1	
Collector / Col-2	6.3	3630	1400	1	for the separated layer
Collector / Col-3	0.32	1465	500	1	for ethyl acetate
Collector / Col-4	1.6	1705	1000	1	for water
Collector / Col-5	6.30	3630	1400	1	for *N*-methylpyrrolidone

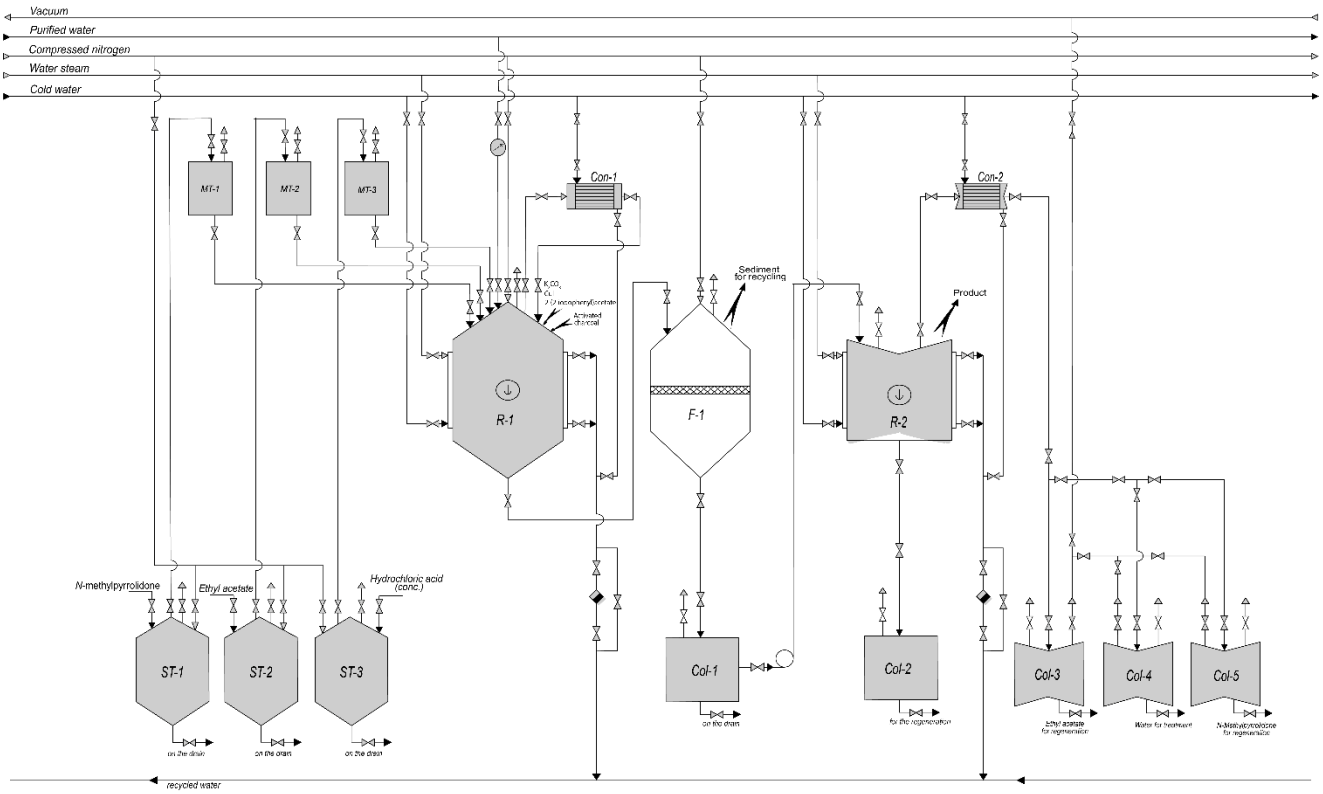

Fig. 5. A principle technological scheme for diclofenac substance production

Thus, the principle technological scheme for the production of the diclofenac substance is shown in Fig. 5. It includes the implementation of the following five technological stages, which are preceded by mandatory auxiliary worksof sanitary preparation of production (AW1) and preparation of raw materials and materials (AW2) (Fig. 6).

At the technological stage I, the synthesis of diclofenac is carried out in a reactor equipped with an anchor stirrer and a shell. 2,6-dichloroaniline and potassium 2-(2-iodophenyl)acetate, anhydrous potassium carbonate, and copper iodide for chemical interaction are added into the reactor R-1 (three reactors R-1 are running in parallel).

N-Methylpyrrolidone is supplied from the measuring tank MT-1. The mixture is heated to 100 °C and stirred for 10 hours using a steam supply into the reactor shell. Then, the mixture is cooled to room temperature using a cold water supply in the reactor shell.

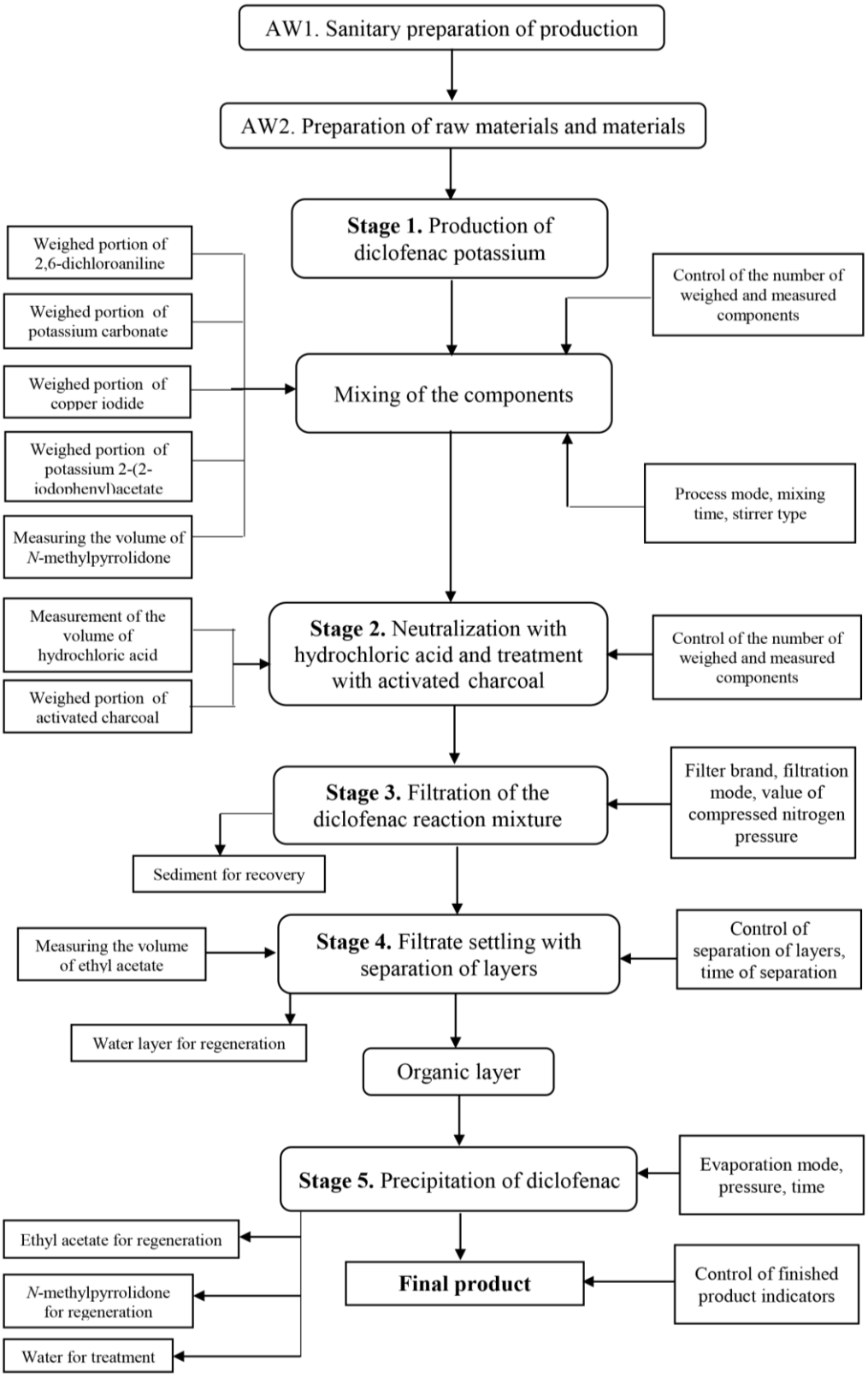

Fig. 6. Technological stages of the production of diclofenac substance

At technological stage II, ethyl acetate is added to the cooled reaction mixture from storage tank ST-2 using measuring tank MT-2. Water is added through a flow meter, and concentrated hydrochloric acid is supported from storage tank ST-3 using measuring tank MT-3. After some time, activated charcoal is loaded, and mixed with a stirrer for 1 hour.

At the technological stage III, the activated charcoal, which has adsorbed the main part of the accompanying impurities, is filtered from the reaction mass of the main product using a filter F-1. The filtrate containing the target substance is collected in the collector Col-1 and moved to the next reactor R-2 (two reactors R-2 are running in parallel), equipped with an anchor stirrer.

At the IV technological stage, the filtrate obtained in reactor R-2 is left to separate the layers. The lower layer is separated, collected in the collector Col-2 and transferred to regeneration.

The solvents are removed using a vacuum distillation *at the technological stage V*. Collectors Col-3, Col-4, and Col-5 are used to collect ethyl acetate, water, and N-methylpyrrolidone, respectively. Pure diclofenac sediment is unloaded from the reactor R-2 and transferred to control of qualitative and quantitative indicators.

The heat carrier and refrigerant quantities, which are necessary to support the temperature regimes for obtaining the diclofenac substance in reactor R-1, were determined using thermal calculations [16–18]. At the first technological stage, it is necessary to heat the reaction mass in the reactor R-1 to a temperature of 100 °C and ensure this temperature regime for 10 hours. As a result, it was established that the heat exchange surface (F = 13.4 m^2 for heating) in reactor R-1 could support the process at the required temperature. In all subsequent technological stages, heat supply is not used. Also, the required amounts of heat-transfer agent (steam) and coolant (water) are determined to support the reactor R-1 operation during the process. Accordingly, the amounts are 35477.15 kg and 13334.96 kg.

Conclusions

As a result of the work carried out, the basis for developing a technology for producing the substance of diclofenac on an industrial scale was proposed based on the data of a laboratory technique [12]. It allows to increase the yield of the target product by up to 61 % compared with the known industrial methods for its production. There are five technological stages for this production, for which the amounts of the necessary raw materials for manufacturing 1 ton of diclofenac has been estimated. The quantity and technological parameters of the primary and auxiliary equipment have been determined, and the support process of thermal conditions has been evaluated. A principle technological scheme of production has been proposed. The advantages of this production method are: increasing the product yield by reducing the number of technological stages and using cheaper raw materials, in particular copper iodide as a catalyst and *N*-methylpyrrolidone as a solvent.

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ОСНОВИ ТЕХНОЛОГІЇ ОДЕРЖАННЯ СУБСТАНЦІЇ ДИКЛОФЕНАКУ

Обґрунтовано та запропоновано основи технології виробництва субстанції диклофенаку, яке складається з п'яти основних технологічних стадій. Запропоновані технологічні аспекти виробництва субстанції диклофенаку дозволяють отримати цільовий продукт із сумарним виходом 61 %. Проведено матеріальні розрахунки для одержання 1 т готової субстанції диклофенаку. Здійснено вибір кількості необхідного технологічного обладнання та запропоновано принципову технологічно схему виробництва диклофенаку.

Ключові слова: 2,6-дихлоранілін; калію 2-(2-йодфеніл)ацетат; міді йодид; диклофенак; основи технології; матеріальні розрахунки; технологічні розрахунки; теплові розрахунки; принципова технологічна схема.