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DEVELOPMENT OF THE TECHNOLOGICAL BASIS FOR THE PRODUCTION OF ACECLOFENAC

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Aceclofenac drugs are widely used in the global therapeutic practice of inflammatory and painful conditions for the treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis in various dosage forms. The basics of the technology of domestic industrial batch production of aceclofenac with a capacity of 110 t/year for the production of a number of effective medicines have been developed. A five-stage production process is proposed that will allow the production of a domestic product with a high yield (~91 %) from commercially available reagents. Material calculations were carried out to determine the consumption rates of raw materials. The types of equipment were selected, and the number of equipment was determined. The basic technological scheme and technological flowchart for the production of aceclofenac are proposed.

Key words: aceclofenac; substance; 2-(*tert*-butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl) amino)-phenyl)acetate; trifluoroacetic acid; acid hydrolysis; basics of technology; technological scheme.

Introduction

Aceclofenac or (2-[2-[2-(2,6-dichlorophenyl) aminophenyl]acetyl)oxyacetate acid (Fig. 1) is a phenylacetate acid derivative by chemical structure. According to the ATC international classification system of medicines, it belongs to two groups: M01A Nonsteroidal anti-inflammatory and anti-rheumatic drugs (M01AB16) and M02AA Nonsteroidal anti-inflammatory drugs for topical use (M02AA25). Aceclofenac was developed as a new non-steroidal anti-inflammatory drug (NSAID) in 1983 by chemical modification of diclofenac to improve gastrointestinal tolerability and reduce side effects [1]. It was first approved for use in medical practice in the European Union in 1992. Since then, it has been approved in 69 countries for use as a NSAID for the treatment of inflammatory and painful conditions such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis [2].

Aceclofenac significantly inhibits both isoforms of the enzyme cyclooxygenase (COX), which is involved in the synthesis of prostaglandins, which are inflammatory mediators causing pain, swelling and fever. It demonstrates high permeability to synovial joints in patients with osteoarthritis and related diseases. Aceclofenac has also been reported to be effective in other painful conditions, such as dental, otolaryngological and gynaecological diseases. It is a drug that is more commonly prescribed in European countries [3]. It is an almost water-insoluble white crystalline powder, but it has a high permeability to body cells, which is why it is classified as a Class II drug substance by the Biopharmaceutical Classification System (BCS) [4]. Aceclofenac is particularly well tolerated compared to other NSAIDs, has a lower incidence of gastrointestinal side effects, and most adverse reactions are mild and reversible, affecting mainly the gastrointestinal system. The parameters of good tolerability lead to a lower withdrawal rate and, therefore, greater efficacy of aceclofenac treatment [5, 6].

In the world, aceclofenac is available in such dosage forms as tablets, ointments, creams, capsules, injections and gels. The well-known brand names of aceclofenac drugs in the world are: Acecgen

(Generics UK), Aflamin, Airtal/Biofenac (Gedeon Richter Plc.), AklofEP (ExtractumPharma), Barcan (Almirall, Sweden), Flemac (Aramis Pharma), Clanza CR (Korea United Pharm., Vietnam), Preservex (Almirall, UK), and Hifenac-P (Intas Pharmaceuticals, India) and others [7].

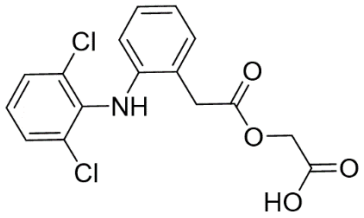

Fig. 1. Chemical structure of aceclofenac

Various studies are being conducted worldwide to develop new and improve existing dosage forms of aceclofenac. In particular, in work [8], rapidly dispersible aceclofenac tablets can be produced by direct pressing using croscarmellose sodium, starch sodium glycolate and crospovidone. In work [9], the authors produced transparent soft capsules of aceclofenac to accelerate absorption. The dissolution rate can be increased by increasing the surface area of the available drug by various methods (micronisation, complexation and solid dispersion). Dispersible and fast disintegrating tablets have been developed for use in paediatrics and geriatrics [10]. The most commonly used methods in this process are freeze-drying, tablet forming and direct pressing. Lyophilised tablets have a very porous structure, which causes rapid penetration of saliva into the pores upon ingestion [11]. The gel dosage form of aceclofenac is not currently widely used in medical practice, but is being widely studied to confirm its effectiveness [12].

However, despite the long life cycle of aceclofenac drugs in the world, the situation on the pharmaceutical market in Ukraine is as follows. According to the State Register of Medicinal Products of Ukraine [13] in January 2024, only a few aceclofenac drugs were registered and approved for use in Ukraine. It should be noted that all drugs are exclusively foreign-made, and the aceclofenac substance is not imported into Ukraine for the production of domestic generic drugs (Table 1).

Table 1

Aceclofenac drugs presented on the pharmaceutical market of Ukraine

Trade name	Dosage of aceclofenac, mg, dosage form	Manufacturer, country
Aertal®	15 mg/1 g, cream	OJSC Gideon Richter, Hungary
	100 mg, film-coated tablets	
	100 mg, powder for oral suspension	
Zerodol	100 mg, film-coated tablets	Ipka Laboratories Limited, India
Eurofenac	100 mg, film-coated tablets	Rivopharm SA, Switzerland
Olfen®-AF	200 mg, modified-release tablets	Korea United Pharm, Inc., Korea
Diclotol®	100 mg, film-coated tablets	Kusum Heltker PVT Ltd, India
	granules, 100 mg, sachets (1 g of granules)	

The world market of manufacturers offering aceclofenac for sale is represented mainly by 21 companies [14], including *Jai Radhe Sales, LGM Pharma, Aarti Drugs, Amoli Organics, Arch Pharmalabs, Om Pharmaceutical Industries, Richter Themis Medicare I Pvt LTD* and others. However, most of these manufacturers are located in China and India.

Therefore, based on the results of the analysis of the assortment of the Ukrainian market of aceclofenac drugs and manufacturers of the substance in the world, it is important to develop the basics of the technology of national industrial production of aceclofenac substance to develop a number of effective medicines based on it. **The purpose of this study** was to analyse the known synthetic methods of aceclofenac production, select a promising laboratory method for the production of this active pharmaceutical ingredient and scale it up to determine the consumption of raw materials for the production of 1 tonne of the substance. Furthermore, in order to select the main and auxiliary equipment, technological calculations should be carried out. On their basis a

principal technological scheme and a technological flowchart for the product production should be proposed.

Materials and research methods

Data on aceclofenac drugs registered on the Ukrainian pharmaceutical market were obtained from the State Register of Medicines of Ukraine [13] in January 2024. Synthetic routes of aceclofenac production were analysed based on the data from the *SciFinder-n* database [15]. The results were processed using the methods of systematisation, analysis, and data comparison. For a given production project, material calculations were made, which at each stage allowed to determine the amount of raw materials required to produce 1 tonne of aceclofenac. Technological calculations made it possible to ensure the selection of equipment and propose a principal technological line for the production of the substance [16–18].

Results and discussion

According to the SciFinder-n database [15], synthetic approaches to the production of aceclofenac, including those used by the above-mentioned companies, can be divided into two main areas. Each of them allows to obtain the product using 1–3 steps, changing reagents and catalytic/non-catalytic/temperature conditions. The first synthetic route involves the conversion of various esters, mainly by hydrolysis reaction (Fig. 2, way *a*) with a target product yield of 78–99 % [19–25]. The second synthetic approach (Fig. 2, way *b*) is based on the interaction of diclofenac or its sodium salt with esters of chloro(bromo) acetic acids, chloro(bromo)acetic acids under different conditions [26–33]. However, for way b, the synthetic part is mostly represented by the production of the product in 2–3 stages, requiring in many cases the use of expensive catalysts, reagents, and temperature control, which significantly increases the duration of the reactions. It also requires thorough purification of the product to pharmaceutical purity. As a result, the total product yield decreases by 35–50 % [26–33].

Therefore, the most optimal is undoubtedly the use of a one-reactor/one-step process according to way a, which allows obtaining a high yield of the target product. Among a number of proposed esters (way a), from which aceclofenac is easily obtained in 78–96 % yield, 2-(tert-butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl)amino)phenyl)acetate is commercially available. The analysis of the reaction conditions for the preparation of aceclofenac from the latter [19–22] allowed to choose a method based on the acid hydrolysis of ester in a strong organic acid medium (Fig. 3).

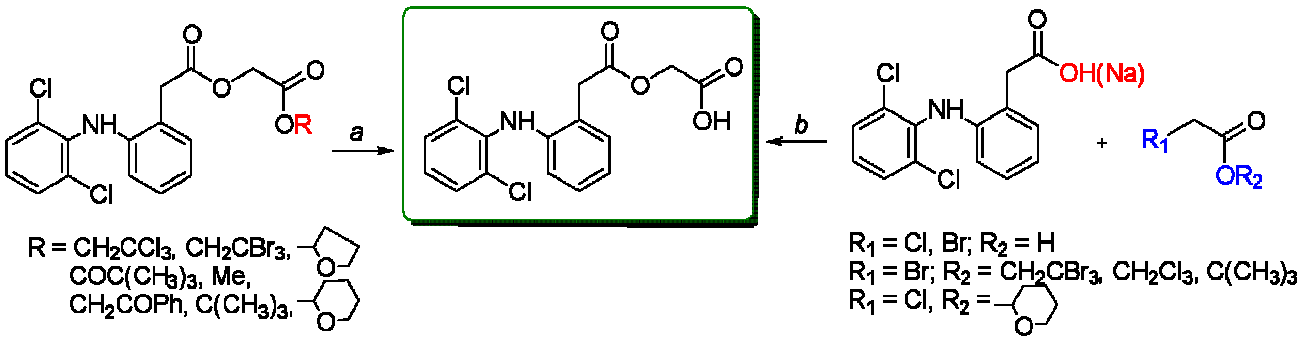

Fig. 2. Synthetic approaches to the production of aceclofenac

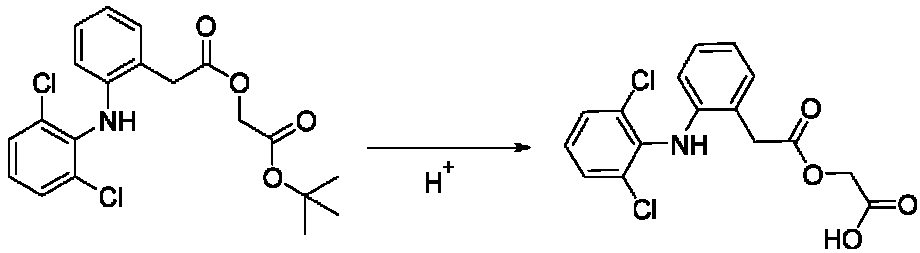

Fig. 3. Method for the preparation of aceclofenac from 2-(tert-butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl)amino)-phenyl)acetate by acid hydrolysis

To scale up the laboratory synthesis of aceclofenac (Fig. 4), we selected the method of preparation [22], which consists in the acid hydrolysis. This method of obtaining the substance involves mixing 10 g of 2-(*tert*-butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl)amino)-phenyl)acetate under a nitrogen atmosphere with 37 g of trifluoroacetic acid at room temperature for 1 hour. After that, the trifluoroacetic acid is evaporated from the mixture under vacuum. The residue is dispersed in water and filtered. After washing and drying at 40 °C, the target product is obtained in 91 % yield. If necessary, aceclofenac can be purified by recrystallisation from toluene.

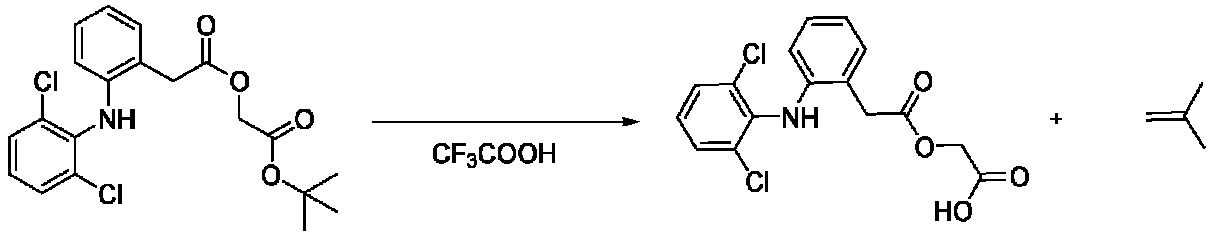

Fig. 4. Scheme of aceclofenac production

It should be noted that the chosen method, as well as other known methods for the conversion of 2-(*tert*-butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl) amino)-phenyl)acetate into the target product [19–33], do not describe the reaction by-products, which is extremely important when designing an efficient, safe, and cost-effective chemical and pharmaceutical production. Taking into account the literature data on the transformation of the tert-butyl residue under acidic conditions [34], a by-product of this hydrolysis reaction is isobutylene, which should be taken into account when designing the production of aceclofenac.

Scaling up the laboratory preparation of aceclofenac [22] is an important step for the subsequent development of national drugs based on it. On the basis of the laboratory method (Fig. 4), the process of aceclofenac production was designed to consist of the following five technological stages with a total yield of 91.3 %:

Stage 1: preparation of aceclofenac, yield 98 %.

Stage 2: distillation of trifluoroacetic acid, yield 99 %.

Stage 3: formation of a suspension and filtration, yield 99 %.

Stage 4: washing the precipitate with water, yield 98 %.

Stage 5: drying of the precipitate, yield 97 %.

The production capacity was accepted as N=110 t/year. The production method was considered to be periodic. On the basis of material calculations [16–18] to produce 1 t of aceclofenac according to the scheme in Fig. 4, the amounts of starting reagents for the proposed industrial production of this substance were determined (Table 2).

Based on the determined material amounts at each stage, technological calculations [16–18] were carried out for particular needs, which allowed to select the types of main and auxiliary equipment, its required quantity, optimal dimensions, volumes and other characteristics (Table 3) from equipment catalogues [16]. The choice of equipment should also take into account the safety requirements of the production process, including the requirements for the materials from which the equipment is made. The selected equipment must be made of stainless steel (e. g., AISI 304/316/316L), which prevents negative impact on product quality.

The selected types of main and auxiliary equipment (Table 3), which are proposed for use at 5 technological stages, were joined by the principle of their operation into an equipment and technological scheme (Fig. 5).

The technological stage 1 trifluoroacetic acid is provided under a nitrogen atmosphere in the reactor R-1 from storage St-1 through the measuring tank M-1 at 20 °C for acid hydrolysis. 2-(*tert*-Butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl)-amino) phenyl) acetate is manually added. Stirring at 20 °C in reactor R-1 is carried out for 1 h using an anchor stirrer. During the hydrolysis of aceclofenac butyl ester, isobutylene is released, which is completely trapped.

Table 2

Amounts of materials required to produce 1 tonne of aceclofenac

Name of substance / purity, %	Weight, kg		Volume, m^3	Density, kg/m^3
	technical product	100 % Product		
2-(*tert*-butoxy)-2-oxoethyl-2-(2-((2,6-dichlorophenyl)-amino)phenyl)acetate / 99.0	1539,6736	1524,2768		
Trifluoroacetic acid / 99.0	3079,3472	3048,5537	2.07	1490
Water	1539,6		1.54	1000

Table 3

Specification of equipment for the production of aceclofenac

Equipment / symbol	Number, pcs.	Volume, m^3	Main dimensions of the equipment, mm		Characteristics
			height	length	
Reactor / R-1	1	2.5	1400	2130	shell, anchor stirrer, $S = 2.08\ m^2$
Measuring tank / M-1	1	0.4	800	370	for trifluoroacetic acid
Storage / St-1	1	2.5	1400	2130	for trifluoroacetic acid
Filter / F-1	1	0.1	400	185	$F = 0.19\ m^2$
Condenser / Con-1	1			1200	$L_{tube} = 1.0$ m, $L_{apparatus} = 1.2$ m (20×2/1)
Collector / Col-1	1	2.5	1400	2130	for trifluoroacetic acid
Collector / Col-2	1	1.6	1200	1820	for filtrate
Dryer / D-1	1				dimensions: 1185×1410×2050 mm

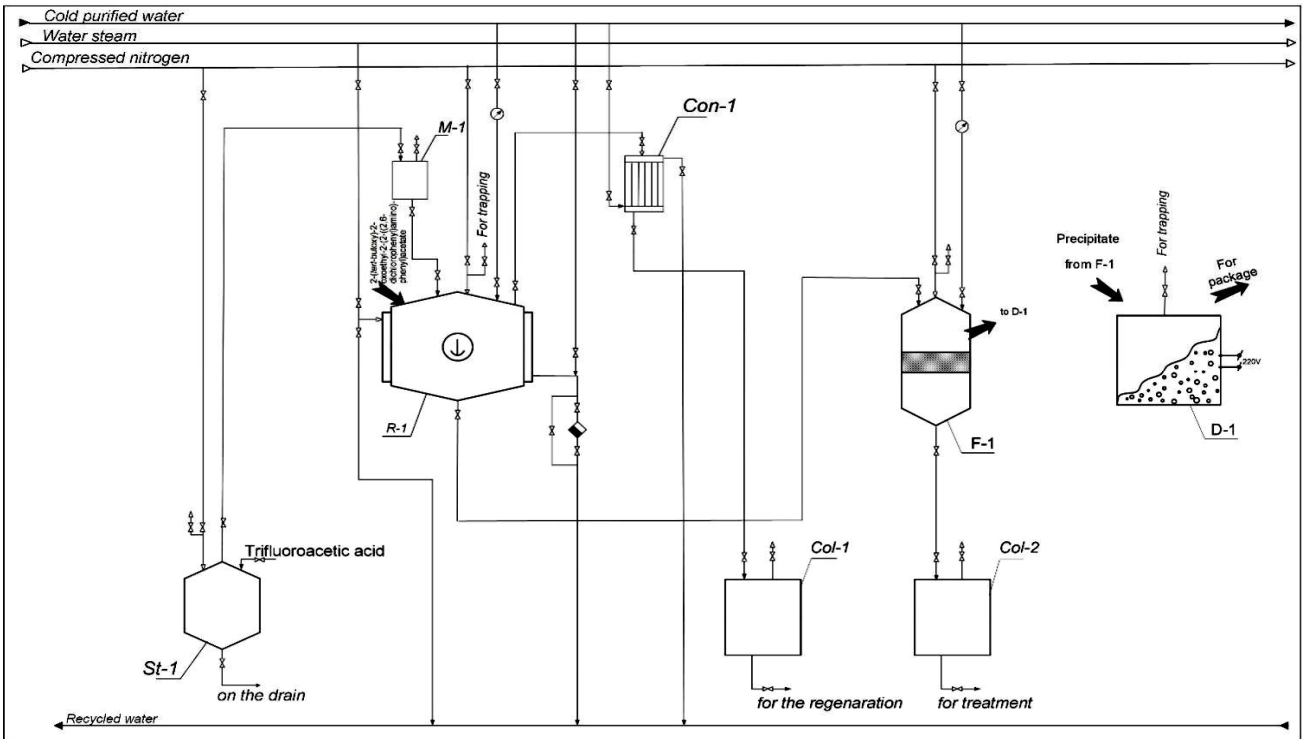

Fig. 5. Principal equipment and technological scheme of aceclofenac production

At the technological stage 2, after the hydrolysis reaction is completed, trifluoroacetic acid is distilled. Steam is fed into the reactor R-1 shell and the reaction mass is heated to a temperature of 72 °C. The trifluoroacetic acid vapour is condensed in the condenser Con-1 and collected in the collector Col-1. Aceclofenac and organic impurities will remain in the cubic residue.

At the technological stage 3, purified water is added to the residue from the previous stage 2 through a flow meter, resulting in the formation of a suspension in the reactor R-1. The suspension is then transferred to the filter F-1, where the aceclofenac precipitate is separated. The filtrate is collected in the collector Col-2.

At the technological stage 4, the precipitate is washed with water, which is added through a flow meter to the filter F-1. After washing, the aceclofenac precipitate is unloaded and transferred to the dryer D-1.

At the technological stage 5, the wet precipitate of aceclofenac is dried, after which the finished product is transferred to the quality control department for quality and quantity control and then to the package.

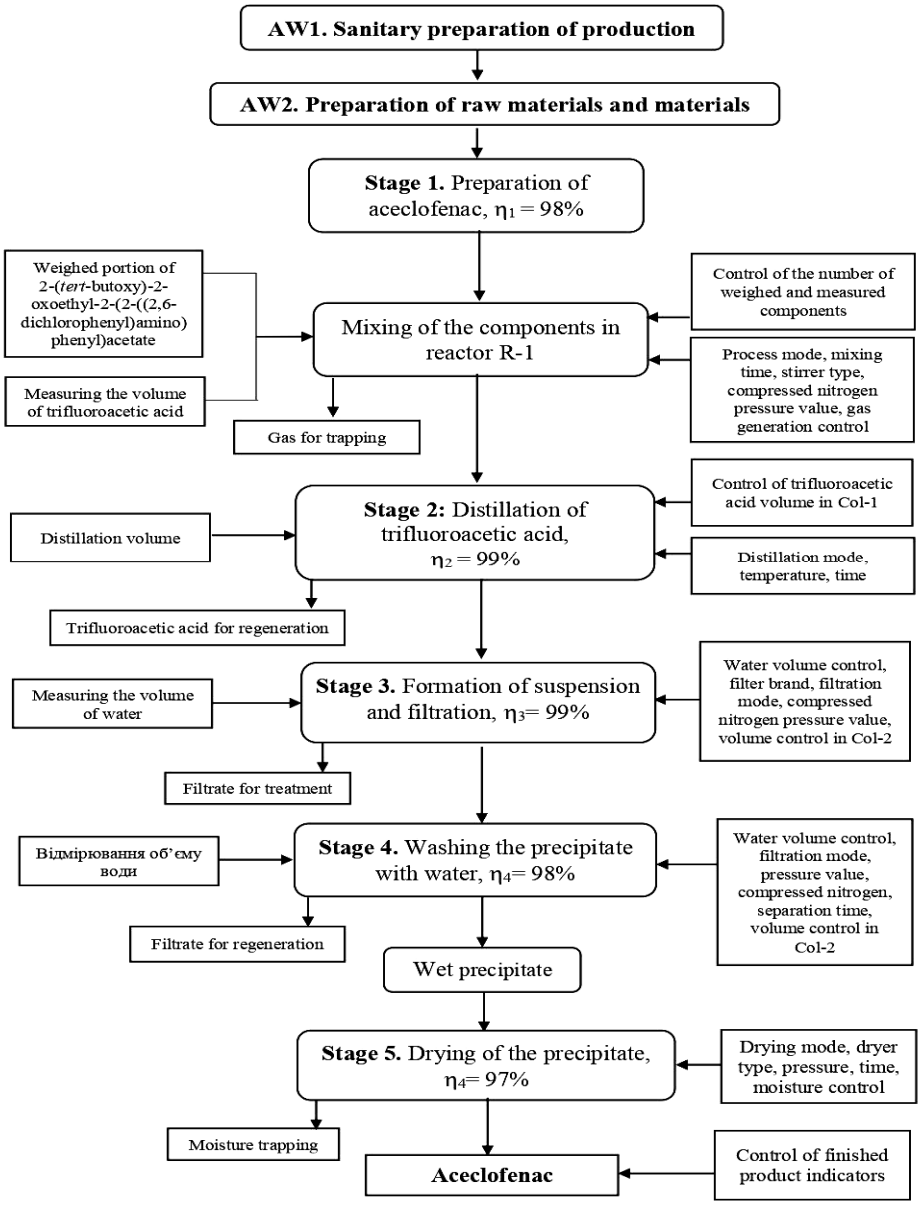

Fig. 6. Technological flowchart of aceclofenac production

For a structured overview of the whole production process, visual representation of each stage of production, understanding the time and raw material requirements of each technological stage, and effective planning of workflows at different stages, a technological flowchart of the aceclofenac substance production project is presented below (Fig. 6). Traditionally, the technological process begins with the mandatory stages of sanitary preparation of production (AW1) and preparation of raw materials (AW2). A mandatory component at all stages is the control of the required process parameters at each stage, which ensures the production of a quality product.

Conclusions

Based on the analysis of data on the known synthesis routes of aceclofenac, a promising laboratory method of its production was selected, for which scaling to the production needs of the Ukrainian pharmaceutical market of substances was carried out. The basics of batch production technology with a capacity of 110 t/year for the production of 1 ton of product were developed. The chosen method of aceclofenac production in five technological stages will allow to produce a national product with a high yield (~91 %) from commercially available reagents in a short time and to regenerate trifluoroacetic acid, returning it to the technological cycle. The proposed technology justifies and takes into account the release of isobutylene during the reaction, which is collected and can be used for various purposes in the future. The determined amounts of raw material allowed to select the types and determine the number of main and auxiliary equipment, which made it possible to propose a principal equipment and technological scheme and a technological flowchart for the production of the product. Aceclofenac preparations have pharmacological advantages and are widely used in the world therapeutic practice in various dosage forms. However, the number of aceclofenac-based medicines on the Ukrainian pharmaceutical market is limited to only 5 trade names. This limits their use in hospital practice. Therefore, the development of the technology of domestic industrial production of aceclofenac substance to obtain a number of effective medicines on its basis is an urgent task of industrial pharmacy.

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РОЗРОБЛЕННЯ ОСНОВ ТЕХНОЛОГІЇ ОДЕРЖАННЯ АЦЕКЛОФЕНАКУ

Препарати ацеклофенаку широко використовують у світовій терапевтичній практиці запальних та больових станів для лікування остеоартриту, ревматоїдного артриту та анкілозуючого спондиліту в різних лікарських формах. Розроблено основи технології вітчизняного промислового періодичного виробництва ацеклофенаку потужністю 110 т/рік для одержання низки ефективних лікарських засобів. Запропоновано виробництво з п'яти технологічних стадій, яке дасть змогу виробляти вітчизняний продукт з високим виходом (~91 %) з комерційно доступних реагентів. Виконано матеріальні розрахунки для визначення норм витрат сировини. Вибрано типи та визначено кількість обладнання. Запропоновано принципову апаратурно-технологічну схему та технологічну блок-схему одержання ацеклофенаку.

Ключові слова: ацеклофенак; субстанція; 2-(*трет*-бутокси)-2-оксоетил-2-(2-((2,6-дихлорфеніл)аміно) феніл)ацетат; трифторацетатна кислота; кислотний гідроліз; основи технології; технологічна схема.