Ф А2.2.1-32-367

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
faculty for foreign citizens' education
pharmaceutical chemistry department

QUALIFICATION WORK

on the topic: «**DEVELOPMENT OF METHODS OF DEXIBUPROFEN DETERMINATION IN MEDICINAL PRODUCTS IN THE FORM OF TABLETS»**

Prepared by: higher education graduate of group Фм19(4,10д)англ-04
specialty 226 Pharmacy, industrial pharmacy
educational program Pharmacy
Maryama BENBRAHIM
Supervisor: associate professor of higher education institution of the department pharmaceutical chemistry, PhD, associate professor Vasyl GRYNENKO
Reviewer: associate professor of higher education institution of the medicinal chemistry department, DSc, professor Ilya PODOLSKY

Kharkiv – 2024 year

ANNOTATION

A spectrophotometric method was developed for the identification and quantitative determination of dexibuprofen in tablet formulations which is based on the intrinsic light absorption of the substance in methanol. The results of the study demonstrate the suitability of the method for pharmaceutical analysis, and the calculated greenness shows that the method is environmentally friendly and will not harm the environment when used in routine analysis.

The qualification work consists of introduction, literature review, experimental part, general conclusions, list of used literature sources, is presented on 41 pages, illustrated with 7 figures, 4 tables, 4 schemas contains 39 sources of literature.

Key words: dexibuprofen, UV spectrophotometry, green method, quality control method

АНОТАЦІЯ

Розроблено спектрофотометричну методику ідентифікації та кількісного визначення дексібупрофену в лікарських засобах в формі таблеток, в основі якого покладено власне світлопоглинання речовиною світла в середовищі метанолу. Результати дослідження демонструють придатність методики для фармацевтичного аналізу, а розрахована зеленість показує, що метод є екологічним і не завдаватиме шкоди навколишньому середовищі при використанні його в рутинному аналізі.

Кваліфікаційна робота складається зі вступу, огляду літератури, експериментальної частини, загальних висновків, списку використаних літературних джерел, викладена на 41 сторінці, проілюстрована 7 рисунками, 4 таблицями, 4 схемами, містить 39 джерел літератури.

Ключові слова: дексібупрофен, УФ-спектрофотометрія, зеленість методики, методика контролю якості

CONTENT

List of abbreviations..... 5

INTRODUCTION..... 6

CHAPTER I. ADVANTAGES AND PLACE IN MODERN THERAPY OF STEREOISOMERIC DRUGS ON THE EXAMPLE OF DEXIBUPROFEN (literature review)..... 9

1.1. Exploring the therapeutic potential of ibuprofen and dexibuprofen..... 9

1.2. Pharmacokinetics and metabolism of dexibuprofen 13

1.3. Dexibuprofen: efficacy and tolerability across various pain conditions 15

Conclusion to Chapter I..... 16

CHAPTER II. PHYSICOCHEMICAL PROPERTIES AND MODERN ANALYSIS METHODS OF DEXIBUPROFEN 17

2.1. Physicochemical properties of dexibuprofen 17

2.2. Methods of dexibuprofen production 17

2.3. Modern methods of dexibuprofen analysis 19

Conclusion to Chapter II 24

CHAPTER III. DEVELOPMENT OF A SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF DEXIBUPROFEN IN TABLETS..... 25

3.1 Object of the study 25

3.2. Equipment and reagents..... 26
3.3. Spectrophotometric method of determination of dexibuprofen..... 26
3.3.1 Determination of the stability of the analysed solution over time..... 29
3.3.2. Method of spectrophotometric determination of dexibuprofen in tablets 31
3.4. Results of quantitative determination of dexibuprofen in tablets..... 31
3.5. Calculation of greenness of the proposed method 37
Conclusion to Chapter III 39

GENERAL CONCLUSION..... 41

LIST OF REFERENCES 42

List of abbreviations

ATP - adenosine triphosphate

CoA - coenzyme A

COX - cyclooxygenase

IR - infrared spectroscopy

LOQ - limit of quantification

NMR - nuclear magnetic resonance spectroscopy

NSAID - Nonsteroidal anti-inflammatory drug

OTC - over-the-counter

PMR - proton magnetic resonance

RSD - relative standard deviation

UV – ultraviolet

INTRODUCTION

Actuality of topic. In recent years, there has been a significant increase in the use of dexibuprofen as an effective anti-inflammatory and analgesic drug in medical practice. Despite its widespread use, there are no monographs in the world pharmacopoeias for finished medicinal products containing standardised methods for the determination of dexibuprofen. This creates an obstacle to quality control of medicines and regulation of their production.

Due to the absence of standard methods of analysis, it is necessary to develop and improve analytical methods for the determination of dexibuprofen in pharmaceuticals, in particular tablets. Among the various analytical techniques, spectrophotometry appears to be a promising and justified alternative.

The use of spectrophotometry for the determination of dexibuprofen has several advantages. Firstly, this method is efficient and sensitive, allowing the detection of even small concentrations of the substance in samples. Secondly, it is fast and can be easily implemented in pharmaceutical laboratories. Third, spectrophotometry is known for its high accuracy and reproducibility.

Thus, the development and improvement of a spectrophotometric method for the determination of dexibuprofen in tablets is of great importance for the pharmaceutical industry and medical practice. This will help ensure the quality and safety of medicines, as well as contribute to the health of patients.

Purpose of work - to develop a spectrophotometric method for the determination of dexibuprofen in tablets for use in routine analysis during quality control of the finished drug product.

The object of the research. «Zotek®-400» (bantches № EDE23003A1, EDE23004A1, EDE23001A1) oral film-coated tablets, manufactured by “Sinmedic”, India, containing dexibuprofen as the active pharmaceutical ingredient in dosage 400 mg.

The subject of the research is the development of a spectrophotometric method for the quantitative determination of dexibuprofen in the tablet dosage form.

Tasks of the work. To achieve the above goal, the following objectives were set:

- to review the literature on the general characteristics, mechanism of action, pharmacological effects and pharmacokinetic parameters of stereoisomers;
- to analyse the literature data on the differences between the racemic drug ibuprofen and its isomer dexibuprofen;
- to analyse the literature on dexibuprofen, its statistical data, evidence base, pharmacological and pharmacokinetic properties;
- to review the physicochemical properties, methods of preparation and methods of analysis of dexibuprofen;
- to develop a method for the quantitative determination of dexibuprofen by UV-spectrophotometry;
- to justify the conditions for spectrophotometric determination (choose a dissolution medium, concentration of active pharmaceutical ingredient, study the stability of solutions);
- to select analytical wavelengths for the identification of the compound;
- to perform quantitative spectrophotometric determination of dexibuprofen in tablets and to perform statistical processing of the results;
- to calculate the greenness of the methodology and determine the environmental impact of the analysis of dexibuprofen by UV-Visible spectrophotometry.

Methods of the research: absorption spectrophotometry in the ultraviolet region of the spectrum, mathematical calculations and statistical processing of the results and the environmental friendliness of the methodology using the AGREE calculator.

The practical value of the results. The developed spectrophotometric method of the determination of dexibuprofen can be used for further analysis of the active pharmaceutical component in medicinal products in form of tablets for identification and quantification.

Elements of scientific research. As a result of the experimental part of the qualification work, a method for the identification and quantitative determination of dexibuprofen was developed, the conditions for the determination of the active pharmaceutical ingredient in finished medicinal products were determined.

The structure of the work. The qualification work consists of introduction, literature review, experimental part, general conclusions, list of used literature sources, is presented on 41 pages, illustrated with 7 figures, 4 tables, 4 schemas contains 39 sources of literature.

CHAPTER I
ADVANTAGES AND PLACE IN MODERN THERAPY OF STEREOISOMERIC DRUGS ON THE EXAMPLE OF DEXIBUPROFEN (literature review)

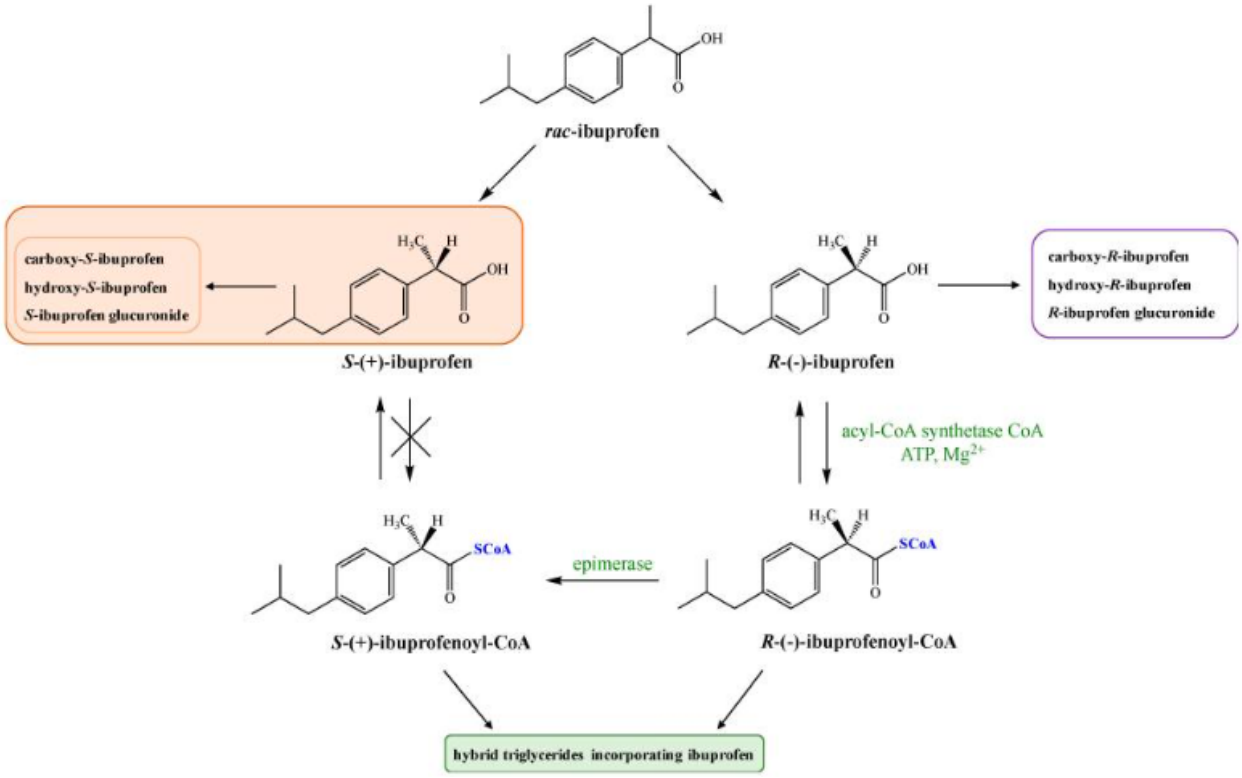
Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to a category of medications that alleviate pain, reduce fever, prevent blood clotting, and decrease inflammation [1]. Generally, NSAIDs are known for their high level of protein binding and small distribution volumes [2]. However, within this group, variations in clearance and half-life are particularly significant. Among NSAIDs, ibuprofen stands out as one of the most commonly used and safest therapeutic options. Ibuprofen was first introduced in the UK in the 1960s and later globally in the 1970s as a prescription drug, typically recommended at a dosage of 2400 mg/day (or higher in the USA) [3]. Presently, ibuprofen is widely employed in numerous countries with minimal side effects, notably avoiding gastric damage often associated with other NSAIDs. Over the past three decades, ibuprofen has been available over-the-counter (OTC) and in generic forms, both as a prescription and non-prescription NSAID with analgesic and antipyretic properties. Its applications extend to the treatment of osteoarthritis, rheumatoid arthritis, and various other painful conditions [4]. These therapeutic effects stem from ibuprofen's ability to block prostaglandin synthesis through non-selective, reversible inhibition of the cyclooxygenase enzymes COX-1 and COX-2 [5]. Despite its high plasma protein binding and low distribution volume, ibuprofen can accumulate effectively in areas of inflammation, such as the cerebrospinal fluid, where anti-inflammatory and analgesic actions are needed.

1.1. Exploring the therapeutic potential of ibuprofen and dexibuprofen

In most commercially available forms, ibuprofen exists as a mixture of diastereoisomers, comprising equal parts of R-(−)-ibuprofen and S-(+)-ibuprofen. The pharmacologically active enantiomer, dexibuprofen, is the dextrorotatory

isomer and was first introduced in Austria in 1994 [6]. Racemic ibuprofen and dexibuprofen exhibit differences in physical, chemical, pharmacological properties, and metabolic profiles [7]. In the past five years, 4836 patients have participated in clinical and post-marketing surveillance trials involving dexibuprofen. Adverse drug reactions were reported in only 3.7% of patients, with three serious adverse reactions (0.06%) recorded. *In vitro* studies have demonstrated that the dextrorotatory isomer exhibits approximately 160 times greater activity in prostaglandin inhibition compared to the R-enantiomer. Additionally, studies on thromboxane generation in clotting blood have confirmed the higher activity of the S-enantiomer compared to the racemate. Therefore, the use of dexibuprofen as a pain reliever would be highly advantageous, particularly since dexibuprofen effectively inhibits both COX-1 and COX-2, while the R-enantiomer only inhibits COX-1, often leading to increased gastrointestinal side effects [8].

Racemic ibuprofen undergoes an unusual metabolic pathway, where the inactive R-(−)-ibuprofen is enzymatically converted to the therapeutically active S-(+) enantiomer. This process may contribute to variability in analgesic effects, including delayed onset of action, and could explain the weak correlation observed between plasma ibuprofen concentrations and clinical responses for acute pain and rheumatoid arthritis. Studies in humans have shown that approximately 50% of the R- (−) enantiomer is metabolically converted to the more active S- (+) enantiomer through the catalytic activity of fatty acyl coenzyme thioesterase in the intestinal tract and liver following oral absorption. However, it's worth noting that the extent of ibuprofen metabolic inversion may vary between 35% and 85% depending on factors such as formulation type, liver condition, concomitant medication, and disease state [9]. This metabolic process begins with the activation of R-(−)-ibuprofen in the presence of coenzyme A (CoA), adenosine triphosphate (ATP), and Mg^{2+} (scheme 1.1).



Scheme 1.1. Metabolic conversion of *R*-(−)-ibuprofen to *S*-(+)-ibuprofen.

Following the AMP-derivative's conversion, CoA esterification is facilitated by acyl-CoA synthetase. Under the influence of -methylacyl-coenzyme A racemase (encoded by the AMACR gene), R-(−)-ibuprofen-CoA undergoes epimerization to yield S-(+)-ibuprofen-CoA, which is then enzymatically hydrolyzed to produce S-(+)-ibuprofen. A crucial aspect of this process involves the substrate's -proton removal followed by non-stereoselective reprotonation. This inversion process can occur both pre-systematically in the gut and within the liver [10].

The resulting thioesters formed from coenzyme A and ibuprofen are subsequently integrated into triglycerides or phospholipids, forming hybrids that may impact the functionality of cell membranes. Notably, literature reports indicate the detection of only the R-enantiomer of ibuprofen in human adipose tissue, exhibiting an elimination half-life of approximately seven days. Studies have demonstrated that oral administration of the pure S-enantiomer allows for a more potent analgesic effect in a shorter duration compared to the racemic mixture.

Enhanced therapeutic efficacy of S-(+)-ibuprofen and significantly reduced side effects have been observed in a cohort of 1400 patients.

As a general approach, it was suggested that a dose ratio of 1:0.75 (ibuprofen to dexibuprofen, respectively) would be necessary to achieve similar pharmaceutical efficacy with dexibuprofen as with ibuprofen. Several clinical trials have been conducted using a dose ratio of 0.5:1, assuming that 50% of the ibuprofen dose corresponds to dexibuprofen. In these trials, dexibuprofen demonstrated therapeutic efficacy comparable to ibuprofen. Comparative studies with other NSAIDs such as diclofenac have indicated that using 75% of the maximum daily dose of dexibuprofen achieved similar efficacy as 100% of diclofenac. Moreover, dexibuprofen has shown clinical efficacy in various conditions including rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis, with better tolerability compared to other NSAIDs such as racemic ibuprofen and diclofenac. Consequently, dexibuprofen could potentially combine the efficacy of diclofenac with the tolerability of ibuprofen. Furthermore, dexibuprofen has been compared to celecoxib, a selective COX-2 inhibitor, for the treatment of hip osteoarthritis, demonstrating comparable efficacy and tolerability profiles [11].

Dexibuprofen exhibits a slower dissolution rate in simulated gastric and enteric juices compared to racemic ibuprofen, leading to improved oral bioavailability. Although pure dexibuprofen offers several advantages, its weak acidity (pKa = 5.2) limits its bioavailability due to its limited solubility in acidic gastric media. According to the Biopharmaceutics Classification System, dexibuprofen is classified as a poorly water-soluble but highly permeable substance (group II). Consequently, its bioavailability is constrained by its poor dissolution, with absorption rate closely mirroring dissolution. These physicochemical properties of dexibuprofen pose challenges *in vivo* models, including incomplete release, food interactions, and high inter-subject variability.

1.2. Pharmacokinetics and metabolism of dexibuprofen

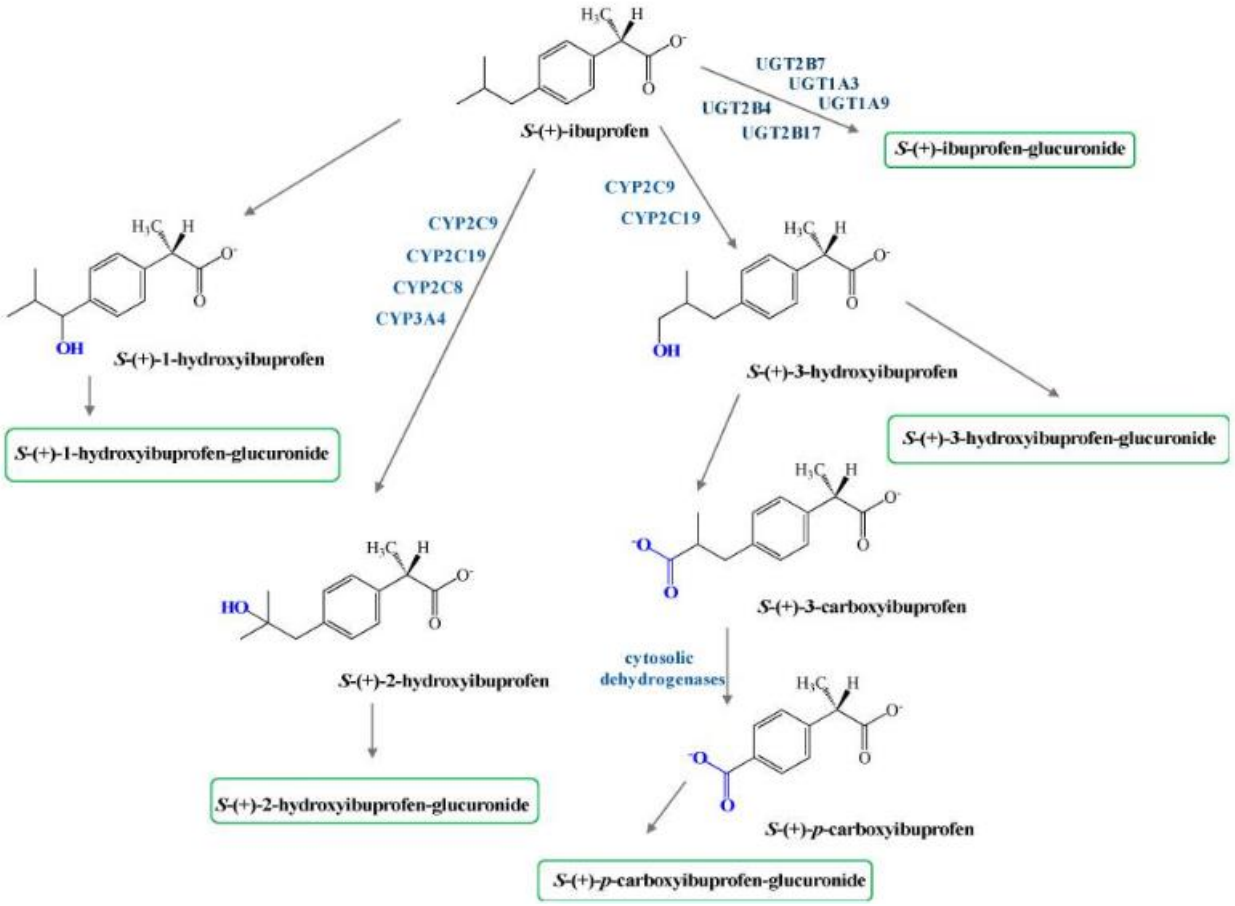
Dexibuprofen, (2S)-2-(4-isobutylphenyl)propionic acid, exerts its therapeutic effects primarily by inhibiting the COX-2 isoform, thereby suppressing prostanoid synthesis in inflammatory cells and resulting in analgesic, antipyretic, and anti-inflammatory actions. Compared to its counterpart, the R-enantiomer, S-(+)-ibuprofen exhibits lower toxicity. Dexibuprofen boasts higher water solubility (68.4 mg/l) and a lower melting point (49–53°C vs 75–77.5 °C dexibuprofen and ibuprofen, respectively), along with improved stability, slower dissolution rate, and enhanced bioavailability.

Currently, dexibuprofen is available in the European Union in tablet form containing 400 mg of the active ingredient [12]. Additionally, several clinical trials are ongoing or have been completed. In the US database, Phase I trials evaluating the safety of dexibuprofen at doses of 300 mg and 200 mg have been approved [13]. A completed Phase I trial assessed dexibuprofen effects on aspirin-treated volunteers. Furthermore, a Phase 3 trial aimed at studying the efficacy and safety of dexibuprofen syrup for fever due to the common cold was completed in 2010. Another Phase IV trial, completed in 2012, compared the tolerability profiles of dexibuprofen and ibuprofen in patients with painful osteoarthritis of the hip or knee. In the European Union database, a completed prospective Phase 3 trial investigated the safety, tolerability, and efficacy of dexibuprofen compared to ibuprofen in patients with osteoarthritis of the hip or knee, showing positive results for dexibuprofen [14].

Most dexibuprofen formulations are designed for oral administration to achieve systemic circulation [15]. After oral intake, dexibuprofen is rapidly and extensively absorbed from the upper gastrointestinal tract, with peak plasma and serum concentrations reached approximately 1–2 hours post-dose. Unbound dexibuprofen concentrations exhibit linear pharmacokinetics at commonly used doses. Although the presence of food delays the time to reach maximum concentration and slightly reduces maximum plasma concentration, it does not affect

the extent of absorption. There is a linear dose-response relationship observed over the dose range from 200 to 400 mg [16].

Phase I metabolism of both enantiomers of ibuprofen involves hydroxylation of the isobutyl chains and subsequent oxidation to form major metabolites such as 2-hydroxyibuprofen and carboxy-ibuprofen. Dexibuprofen has been reported to exhibit preference over the R-enantiomer in both phase I and II metabolism (scheme 1.2.)



Scheme 1.2. Oxidative metabolism of dexibuprofen.

Protein binding is enantioselective, with dexibuprofen showing decreased binding compared to the R-enantiomer, potentially leading to higher transfer into blister fluid or synovial fluid, where it exerts its pharmacological activity.

Major metabolites are excreted in the urine, with around 25% and 37% of an administered dose accounted for by 2-hydroxyibuprofen and carboxy-ibuprofen, respectively. Metabolism of S-(+)-ibuprofen is predominantly catalyzed by

cytochrome isoform CYP-2C9. Gender-related differences in pharmacokinetics have not been observed, except for a higher volume of distribution in adult females compared to males [17].

1.3. Dexibuprofen: efficacy and tolerability across various pain conditions

Numerous randomised clinical trials have shown high clinical efficacy and good tolerability of dexibuprofen in patients with toothache, headache, gonarthrosis, osteoarthritis, rheumatoid arthritis, and dysmenorrhoea.

In arthritis, dexibuprofen at a dose of 800 mg had the same analgesic effect as 200 mg of celecoxib, and 200 mg of dexibuprofen relieved pain as 400 mg of ibuprofen, with dexibuprofen showing better tolerability [18].

There is also evidence of the effectiveness of dexibuprofen in the treatment of acute postoperative pain [19].

According to the results of a randomised, double-blind study involving patients experiencing acute visceral pain as a result of primary dysmenorrhoea, dexibuprofen showed dose-dependent effective analgesia.

The effect of the drug was equivalent to that of ibuprofen, which was used at twice the dose [20].

In toothache, the effect of 200 mg of dexibuprofen is equivalent or even superior to that of 400 mg of ibuprofen racemate [21].

Thus, the active enantiomer dexibuprofen in various conditions accompanied by moderate pain showed equal efficacy compared to a double dose of racemic ibuprofen.

The data on the use of dexibuprofen in patients with rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the knee and hip joints, back pain, and dysmenorrhoea are summarised in a clinical review by W. Phleps. High clinical efficacy and good tolerability of dexibuprofen in all these conditions have been shown [22].

There is information about the successful use of dexibuprofen in paediatric practice. For example, S. Muralidharan studied the comparative efficacy and safety of dexibuprofen and ibuprofen in children with fever caused by upper respiratory tract infection. There were no statistically significant differences in the antipyretic effect (maximum temperature reduction, mean time to onset and duration of effect) of dexibuprofen at a dose of 5 mg/kg and ibuprofen at a dose of 10 mg/kg. There were also no significant differences in drug tolerability [23].

Clinical trials conducted by Ukrainian scientists have demonstrated the high efficacy of dexibuprofen at a dose of 400 mg in the treatment of headache in patients with migraine, tension headache, trauma-related headache, and cervicogenic headache [24].

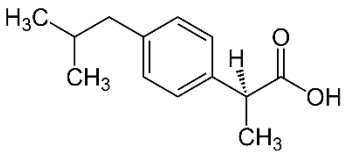
Conclusion to Chapter I

1. The literature shows that dexibuprofen is an active enantiomer of ibuprofen, which has advantages due to its higher efficacy and better tolerability. Clinical trials and post-marketing surveillance demonstrate the efficacy of dexibuprofen in a variety of conditions with minimal adverse events reported.
2. The pharmacokinetics of dexibuprofen include rapid absorption from the gastrointestinal tract, linear kinetics at usual doses and predominant COX-2 inhibition.
3. The scientific literature confirms the effectiveness of dexibuprofen in various pain conditions, including arthritis, postoperative pain, dysmenorrhoea and headache. Dexibuprofen demonstrates comparable or higher analgesic effect than racemic ibuprofen at lower doses and with better tolerability. Its efficacy extends to paediatric use and is promising in the treatment of migraine and tension-type headache. Clinical studies highlight its efficacy and safety profile in various patient populations.

CHAPTER II
PHYSICOCHEMICAL PROPERTIES AND MODERN ANALYSIS METHODS OF DEXIBUPROFEN

2.1. Physicochemical properties of dexibuprofen

DEXIBUPROFEN



(2S)-2-(4-isobutylphenyl)propionic acid

$C_{13}H_{18}O_2$ M.w. 206.28 g/mol

Dexibuprofen is easily soluble in methanol, acetone (less than 0.1 mg/ml) and practically insoluble in water (68.4 mg/l).

Melting point of substance is 49-53ºC [25].

2.2. Methods of dexibuprofen production

Ibuprofen was first synthesised in the UK in 1967 by Boots, and after pharmacological study it was recommended as a treatment for rheumatoid arthritis, osteoarthritis and other inflammatory diseases.

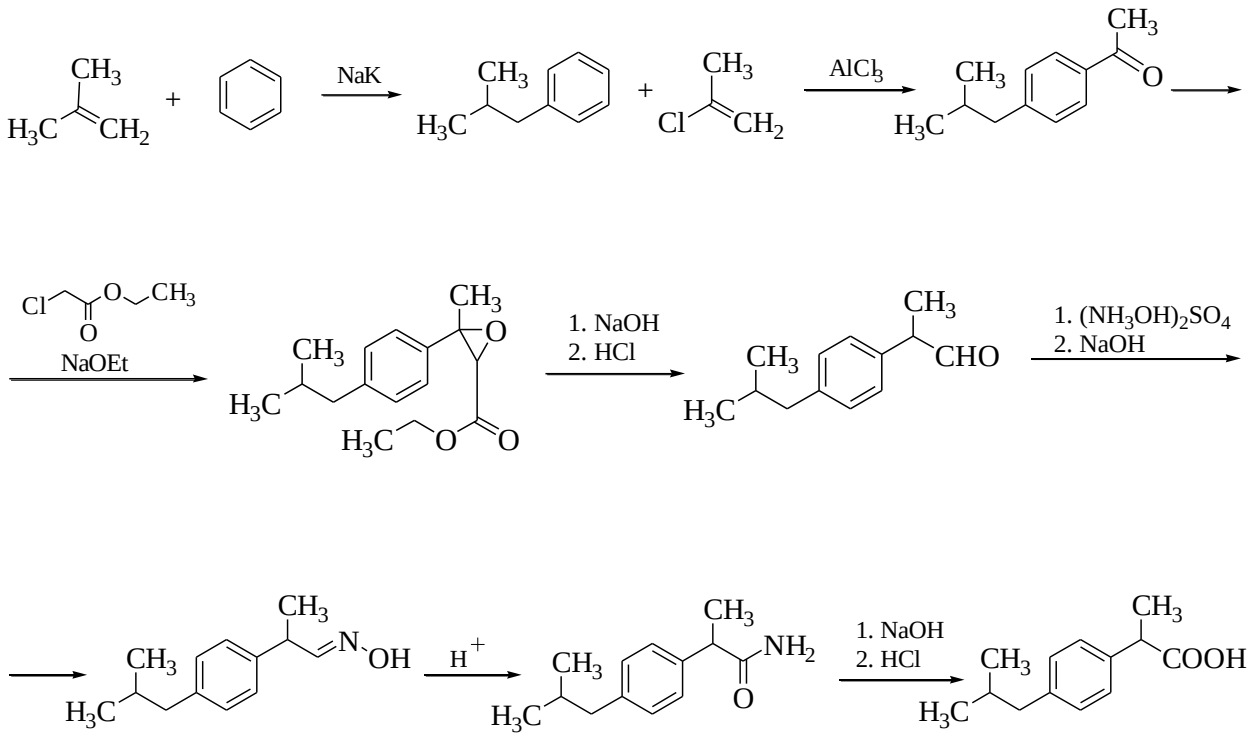
By asymmetric esterification of racemic ibuprofen with chiral amides of (S)-lactic acid, a mixture of (S,S)- and (R,S)-esters is obtained, which is easily separated on a silica gel column. The highest yield of the (S,S)-distearomer is achieved when pyrrolidine lactamide and toluene are used as solvents:

$$\frac{(S,S)}{(R,S)} = \frac{85}{15}.$$

The hydrolysis of the obtained (S,S)-esters with acetic-hydrochloric acid mixture in 80% yield yields the (S)-enantiomer of ibuprofen, dexibuprofen. The

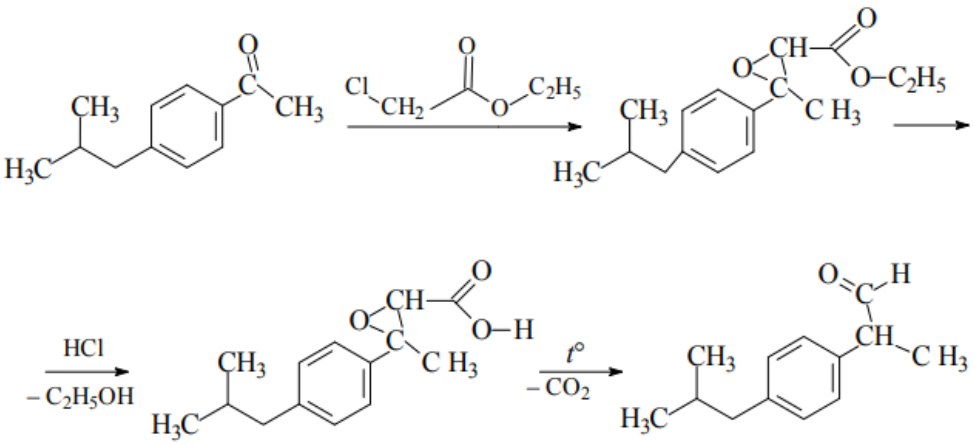
experimental data obtained are consistent with the evaporation data based on the MM2 mechanical model of force fields.

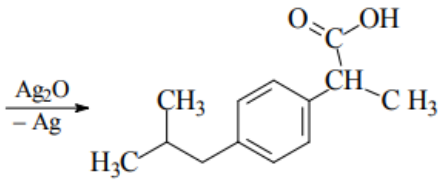
According to the literature [26], the synthesis of ibuprofen is carried out according to the following scheme 1.3:



Scheme 1.3. Synthesis of ibuprofen

Another synthesis pathway for ibuprofen is also known, shown in Scheme 1.4:





Scheme 1.4. Synthesis of racemic ibuprofen

The enantioselective separation of (+/-)-ibuprofen compositions was successfully carried out. The efficiency of separation by capillary electrochromatography and nanofluid chromatography was studied and compared; the resolution of (+/-)-ibuprofen was 2.45 and 2.97 for capillary electrochromatography and nanofluid chromatography, respectively; the number of theoretical plates for thiourea was 41600 N/m for capillary electrochromatography. The chiral monolithic capillary columns for capillary electrochromatography and nanofluid chromatography were prepared by bonding β-cyclodextrin modifier to a monolithic acrylic phase.

There are data on the distribution and analysis of ibuprofen enantiomers by high-performance liquid chromatography, which is used to reduce side effects and study metabolic processes.

In order to reduce toxicity and increase the anti-inflammatory effect of ibuprofen in cartilage, condensation of 4-i-Bu-C_6H_4CHMeCOR with α-diethylaminoethanol in dichloromethane in the presence of triethylamine and methylation with methyl bromide in ace-tonic acid was synthesised - a quaternary ammonium derivative of ibuprofen. The structure was confirmed by IR, PMR, and 13C NMR data [27].

2.3. Modern methods of dexibuprofen analysis

The identification of dexibuprofen is based on its physicochemical properties and chemical structure, so the same methods are used for the determination as for

ibuprofen, except for the determination of specific optical rotation, which is a test for determining the identity and purity of the substance.

Also, melting point data is used to confirm the frequency and determine the S-(+) isomer of ibuprofen, which should be 49-53 ◦C (75-77.5 ◦C for the melting point of the ibuprofen racemic mixture).

A high-performance liquid chromatography method with a diode array detector was developed and validated for the determination of dexibuprofen in dexibuprofen tablets using an omocoydic chiral stationary phase (Ultron ES-OVM). The mobile phase consisted of 0.025 M potassium dibasic phosphate (pH 4.5)-methanol-ethanol (85:10:5 v/v). The method was tested for specificity, linearity, range, precision, accuracy and reliability. The method was enantiomer specific for the determination of dexibuprofen [S - (+) - isomer of ibuprofen] in the presence of R - (-) - isomer of ibuprofen in bulk drug, pharmaceutical dosage form and under stress degradation. The method was linear in the range of 15-35 mg/ml with r^2 = 0.9995; precision and accuracy were acceptable with % RSD <2.0%. The method was found to be specific, precise, accurate, reliable and indicative of stability and can be successfully applied to the routine analysis of dexibuprofen in substance and finished dosage form.

It was proposed to determine the enantiomeric purity by optimised chiral liquid chromatography. A Chiralcel OD column was used as the chiral stationary phase, and a 100:1:0.1 mixed eluent of hexane, isopropanol, and acetic acid was used as the mobile phase at a flow rate of 1.0 mL/min. Each data was obtained from the average of at least three different experiments for each sample, and the relative standard deviation was very small. The optical purity values of most of the generic dexibuprofen products used in the study were above 99 % [28].

For identification and quantification, a spectrophotometric method in the ultraviolet region was proposed. Spectral analysis shows the maximum absorption of dexibuprofen in methanol at 222 nm. It was found that the linearity lies in the concentration range from 2.5 to 20 μg/ml. The molar absorbance was found to be

9.1 x 103 l/mol/cm. The assay was found to be in good agreement with the declared content of the active substance in the tablets on the label [29].

The monograph on dexibuprofen is not included in any Pharmacopoeia of the World, so to review possible pharmacopoeial methods for the analysis of the S - (+) - isomer of ibuprofen, we relied on the monographs of the racemic form - ibuprofen.

Ibuprofen is identified by thin-layer chromatography using solvent systems:

- chloroform - acetone (4: 1); Rf = 0.46;

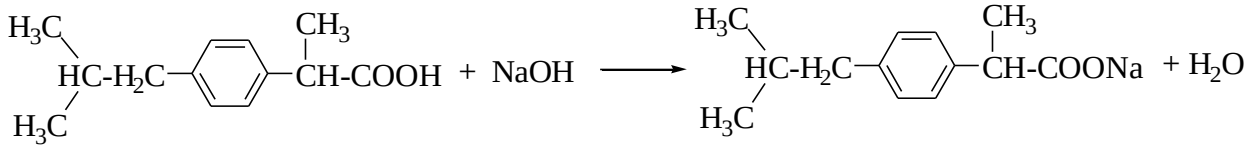
- ethyl acetate; Rf = 0.54;

- ethyl acetate - methanol - ammonia concentrated solution (80:10:10); Rf = 0.18.

- anhydrous acetic acid - ethyl acetate - hexane (5:25:75).

The SPhU monograph [30] recommends identifying ibuprofen by chromatographing a solution of the test substance and a solution of the ibuprofen FSS under the same conditions. The mobile phase is a solvent mixture of anhydrous acetic acid - ethyl acetate - hexane (5:24:71). The plates are developed by spraying with a solution of potassium permanganate in dilute sulfuric acid and heated at 120°C for 20 minutes. When viewed under UV light at 365 nm, the chromatogram of the test solution should show a main spot at the level of the main spot on the chromatogram of the reference solution, corresponding to its size and colour.

The official method of quantification, according to the monograph of the State Pharmacopoeia of Ukraine, of ibuprofen as an acid is determined by the alkalimetric method. Dissolve a weight of the substance in methanol and titrate with 0.1 M sodium hydroxide solution. The indicator is phenolphthalein:



Ibuprofen in tablets (after extraction from the tablet mass with chloroform) is titrated in ethyl alcohol neutralised with phenol-phthalein with 0.1 M sodium hydroxide solution potentiometrically.

This method was also used to study the rate and degree of release of ibuprofen from solid fat and polyethylene oxide base No. 1 (VEO 4000 - VEO 1500 - VEO 400 4: 3: 3); No. 2 (VEO 4000 - VEO 1500 - VEO 400 1: 8: 1); No. 3 (VEO 4000 - VEO 400 6: 4) in the study of rectal forms of ibuprofen.

The conditions for the titrimetric determination (RS)-2-[4-(2-methylpropyl)phenyl]-propionic acid with the establishment of the equivalence point using bromothymol blue were developed. The effective pH value of ibuprofen in a 0.1 M sodium dodecyl sulfate solution was found to be 6.39±0.02 using the pH-metric titration method. The limiting solubility of ibuprofen is 400 mg/100 g of 0.1 M sodium dodecyl sulfate solution, which is sufficient for its reliable determination by the acid-base titration method. The calculations have shown that when titrating ibuprofen solutions with a concentration of 3.0-4.0 mg/ml, the pH value at the equivalence point is in the range of 9.23-9.93. The data on the pH shift of sulfophthalein indicators in aqueous micellar solutions of sodium dodecyl sulfate show the possibility of using bromothymol blue as an indicator, the pH value of which is 9.21.

The determination of ibuprofen in combination pharmaceuticals with other NSAIDs and other components is carried out by chemical approaches using UV-Vis absorption spectrophotometry, as it is reported to be a simple alternative to the use of separate models for each component. For example, in the joint determination of a mixture of paracetamol, ibuprofen and caffeine, spectra were recorded at several concentrations within their linear ranges and used to calculate a calibration mixture between 200 and 400 nm at 1.0 nm intervals in methanol: 0.1 mol/l HCl (3:1). Partial least squares regression, genetic algorithm combined with least squares regression and principal component artificial neural network were used for chemical analysis of the data, and the parameters of chemical procedures were optimised.

The chemiluminescence method was used for the quantitative determination of ibuprofen in tablets by inhibiting the chemiluminescence of the H_2L - H_2O_2 - Hb system. RSD = ± 1.56 % (δ = -0.75 %) and RSD = ± 1.68 % (δ = -0.35 %) for Ibuprofen and Nurofen tablets, respectively, LOQ $3\text{-}10^{-5}$ M mol/l.

Given the high sensitivity, the proposed method is promising for further research on its use for the determination of small amounts of ibuprofen in wash water during the control of equipment washing at pharmaceutical enterprises [31].

The analytical performance of these chemometric methods was characterised by relative prediction errors and recoveries (%) and compared with each other [32].

To isolate ibuprofen and its metabolites from blood plasma, a solid-phase extraction method is used. The eluate was chromatographed on Chiral AGP-α 1 columns using a mobile phase of phosphate buffer solution (pH 7.0) - isopropanol 98:2, mobile phase flow rate 0.9 ml/min. Detection was performed spectrophotometrically at a wavelength of 225 nm. Naproxen was used as an internal standard.

Liquid-liquid extraction was also used to isolate ibuprofen from blood plasma. For example, it was proposed to use a mixture of hexane-isopropyl alcohol (95:5) in the presence of 1 M hydrochloric acid (internal standard - naproxen) as an extractant. The chromatographic analysis was performed on a Chromsil-l00-5CHI-TBB analytical column with a mobile phase of hexane - methyl tert-butyl ether - isopropanol (88: 12: 1.5) at a speed of 1 mL/min, detection was spectrophotometric at a wavelength of 220 nm.

A similar sample preparation method was described for extraction with cyclohexane in the presence of 3 M hydrochloric acid (without internal standard). The separation of stereoisomers was performed on a Chiral AGP-α 1 column using the following mobile phase composition: 990 ml of phosphate buffer solution (pH = 6.9), 10 ml of acetonitrile and 204 μl of N, N-dimethyloctylamine.

To determine the efficacy of ibuprofen in capsules, capillary electrophoresis was used. A capillary with an internal diameter of 50 μm and a UV detector at a

wavelength of 214 nm were chosen. When using a phosphate buffer solution (pH 6.86) and 11 kV, the determination is performed within 6 minutes [33].

A method for the spectrophotometric determination of ibuprofen in tablets, creams and syrups has been developed [34]. The method is based on the measurement of fluorescence intensity at λ abs. = 263 nm and λ sp. = 288 nm. The calibration curve is linear in the concentration range from 2 mg/l to 73 mg/l. Other drugs and excipients in various forms do not interfere with the determination, except for chlorzocazone. The relative standard deviation is in the range of 0.003-0.017. The measure of accuracy is 95.0% - 102.0%.

The spectrophotometric determination of ibuprofen in medicinal products is also carried out in a 0.1 M sodium hydroxide solution, with potassium ferricyanide as a reference standard. Measure the absorption of the test solution and the potassium ferricyanide reference solution using a spectrophotometer at a wavelength of 259 nm. The results are calculated according to the formula by introducing a conversion factor. The proposed method allows to increase the reproducibility of the determination results, the sensitivity of the analysis, reduce the complexity of the determination, the analysis error, eliminate the use of toxic reagents and unify the analysis methods [35].

Conclusion to Chapter II

1. The literature data on the physicochemical properties of dexibuprofen, peculiarities of the pure isomeric form of ibuprofen and purification methods were analysed.
2. The literature data on possible chemical and physicochemical methods of dexibuprofen analysis, including capillary electrophoresis, chemiluminescence, titrimetric determination, chromatographic methods and spectral.

CHAPTER III
DEVELOPMENT OF A SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF DEXIBUPROFEN IN TABLETS

The literature describes the determination of dexibuprofen using physicochemical methods, including liquid chromatography, capillary electrochromatography, and high-performance thin-layer chromatography. Spectrophotometric determination has also been studied using chemometrics and a derivative approach [36]. It is noteworthy that the differentiation and smoothing algorithms for UV-visible spectrophotometry were not explicitly stated in these studies, whereas they always play an important role in determining the sensitivity and accuracy of derivative methods.

3.1 Object of the study

The object of the study was «Zotek®-400» (bantches № EDE23003A1, EDE23004A1, EDE23001A1) oral film-coated tablets manufactured by Sinmedic, India, containing dexibuprofen as the active pharmaceutical ingredient.

Figure 1.1. Photo illustration of the object of study

1 film-coated tablet, contains dexibuprofen 400 mg

Excipients: microcrystalline cellulose, colloidal silicon dioxide, talc, calcium carmellose, coating composition: hypromellose, titanium dioxide (E 171), talc, dichloromethane, isopropyl alcohol.

Dexibuprofen with a purity of 99.9% was used as a standard sample for the study.

3.2. Equipment and reagents

Reagents that meet the current requirements of the Pharmacopoeias of the world and International Quality Standards were used in the study [30, 37, 38].

The study was conducted using calibrated, metrologically certified equipments: electronic scales (model ABT 120-5DNM, manufactured by KERN&SOHNGmbh (Germany), spectrometer Specord 200, manufactured by AnalitikZena (Germany), class A measuring utensils and high-purity reagents.

3.3. Spectrophotometric method of determination of dexibuprofen

Spectrophotometric methods, despite their low selectivity, are still widely used in the analysis of drugs due to their comparative availability, cost-effectiveness, simplicity, and good accuracy. It is known that most medicinal substances have their own light absorption in the ultraviolet region, and some of them enter into chemical reactions that lead to the formation of coloured compounds. This makes it possible to develop new methods based on the optical properties of compounds and aimed primarily at determining the active components without separating them. As a result, the cost of sample preparation is reduced and the expressiveness of analysis is increased, which is important given the high flow of medicines to the pharmaceutical market. Spectrophotometry is a pharmacopoeial method included in the State Pharmacopoeia of Ukraine [30], the European Pharmacopoeia [37], the US Pharmacopoeia [38] and all national pharmacopoeias. The share of spectrophotometric methods in different pharmacopoeias ranges from 5% (in the German Pharmacopoeia) to 15-22% (in the European, American, Ukrainian and other pharmacopoeias), and there is a tendency for their increase.

The use of spectrophotometry for the determination of dexibuprofen is based on the absorption of electromagnetic radiation by chromophore (C = C, C = O) and auxochromic (OH) groups.

To determine the wavelength that is analytical for the identification of the compound and suitable for the quantitative determination of dexibuprofen in dosage form, the absorption spectrum of the dexibuprofen solution in methanol was analysed in the wavelength range from 220 nm to 400 nm (Fig. 3.1).

Figure 3.1. Ultraviolet absorption spectrum of 0.05% methanolic solution of dexibuprofen

The spectrum shows three clear absorption maxima at 258 nm, 264 nm and 272 nm, which are analytical and can be used for the identification of the compound in the substance and the finished drug product.

To evaluate the suitability of the spectrophotometric technique as a method for the quantitative determination of dexibuprofen, the linearity of the dependence of the absorption on the concentration of the drug solution was assessed. The study was carried out for dexibuprofen solutions in methanol in the concentration range from 0.003 to 0.050 mg/mL, which is from 80 % to 120 % of the concentration level of the original dexibuprofen solution (Fig. 3.2-3.4).

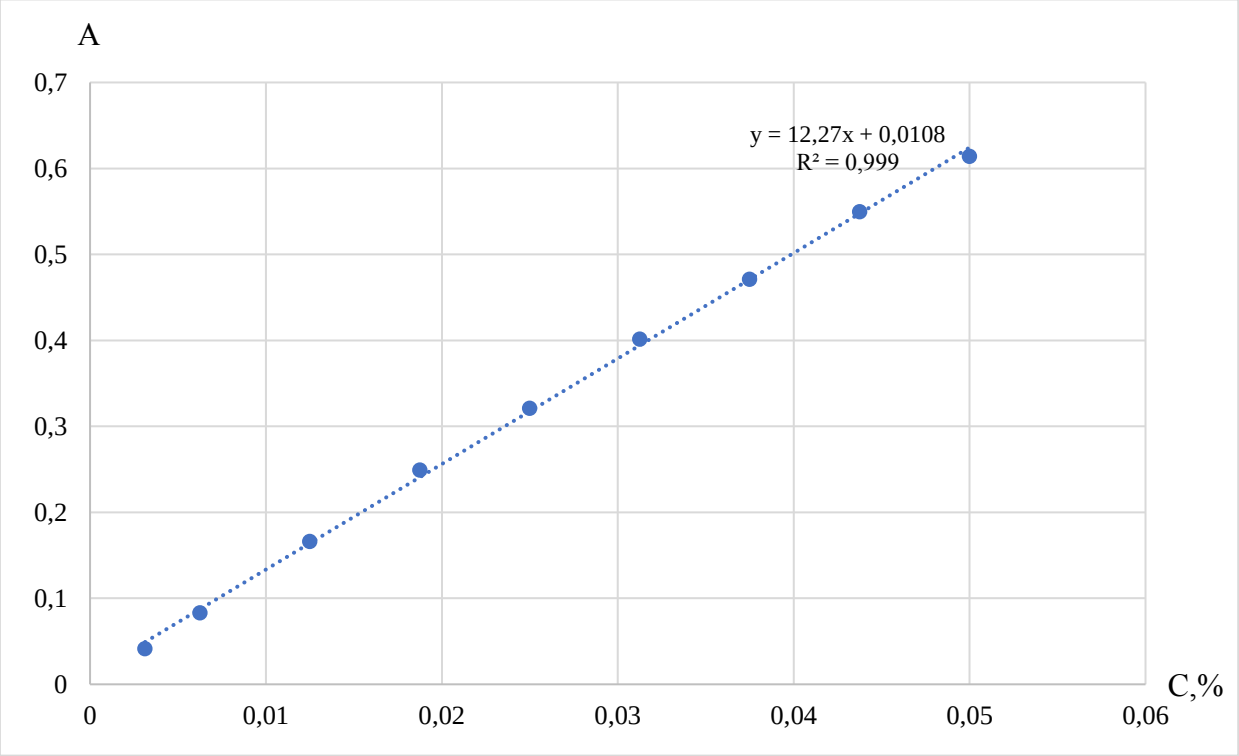


Figure 3.2. Obedience of the light absorption law of methanol solutions of dexibuprofen at 258 nm

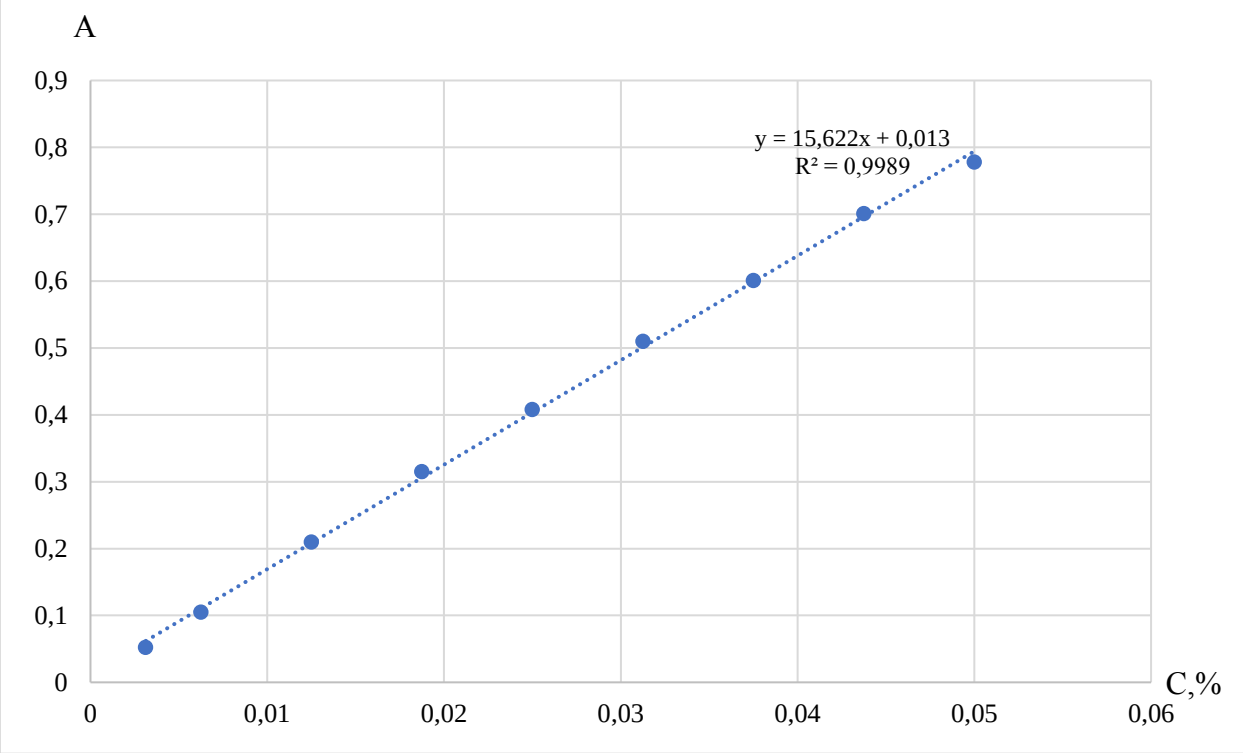


Figure 3.3: Obedience of the light absorption law of methanol solutions of dexibuprofen at 264 nm

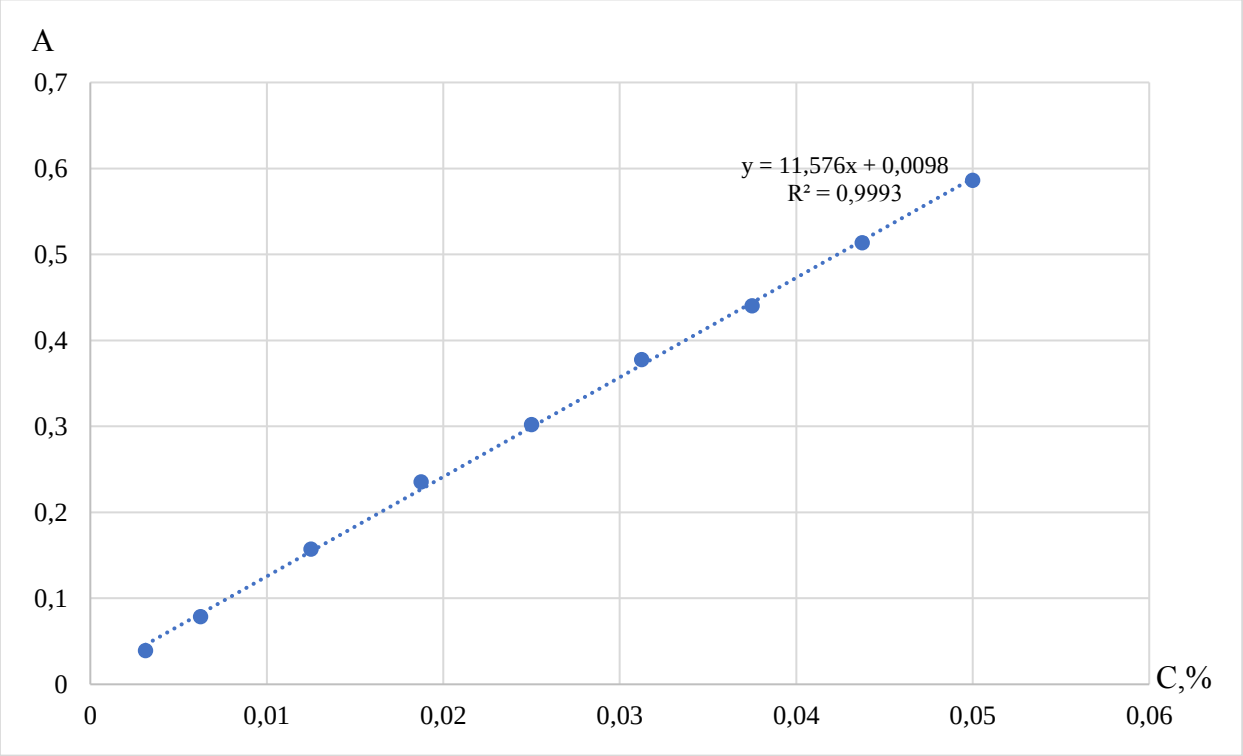


Figure 3.4. Obedience of the light absorption of methanol solutions of dexibuprofen at 272 nm

For the quantitative analysis of dexibuprofen in further measurements, it was decided to carry out at a wavelength of 258 ± 2 nm, which is more specific for this compound. The dependence of the absorption of dexibuprofen solution on its concentration at the selected wavelength obeys the Bouguer-Lambert-Beer law in this concentration range, with a correlation coefficient of 0.999.

3.3.1 Determination of the stability of the analysed solution over time

For further use of the methodology, the stability of the solutions over time was studied. The stability of the solutions was determined for 1 hour with an interval of 10 minutes by measuring the absorption on a spectrophotometer "Evolution 60 s" in the "Kinetics" mode (Table 3.1, Fig. 3.5).

Table 3.1.

Study of the change in the absorption of dexibuprofen methanol solution at 258 nm with time

Solution	Time, min						
	0	10	20	30	40	50	60
0.05% methanolic solution of dexibuprofen RS	0,615	0,614	0,614	0,615	0,615	0,615	0,616

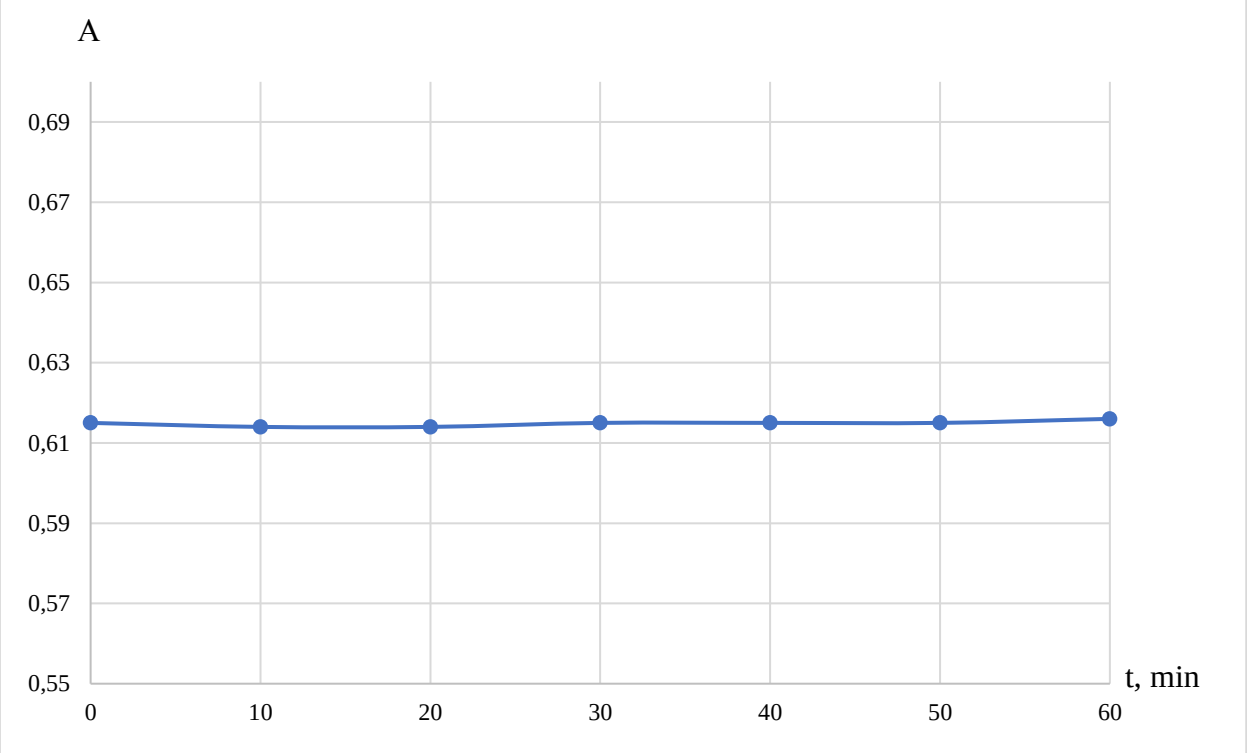


Figure 3.5. Investigation of the change in absorption with time of 0.05% methanolic solution of dexibuprofen at 258 nm

The results of the study of the change in absorption over time showed that the methanol solution of dexibuprofen is stable for 1 hour.

3.3.2. Method of spectrophotometric determination of dexibuprofen in tablets

The test is carried out in accordance with the requirements of the State Pharmacopoeia of Ukraine, 2.2.25.

Test solution. A weight of powdered powdered tablets equivalent to 50.0 mg of dexibuprofen is placed in a 100 ml volumetric flask, dissolved in methanol R and the volume of the solution is brought to the mark with the same solvent and stirred.

Reference solution. Place 50.0 mg (exact weight) of dexibuprofen RS in a 100 ml volumetric flask, dissolve in methanol R and bring the volume of the solution to the mark with the same solvent and mix.

Measure the absorption of the test solution and the reference solution using a spectrophotometer at a wavelength of 258 ± 2 nm in a cuvette with a layer thickness of 10 mm, using methanol R as a compensation solution.

Calculation. The content of dexibuprofen (X) in tablets, in mg, is calculated by the formula:

$$X = \frac{A_1 \cdot m_0 \cdot 100 \cdot P \cdot m_{av.tab.}}{A_0 \cdot m_1 \cdot 100}$$

where: A_1 - absorption of the test solution;

A_0 - absorption of the reference solution;

P - content of the main substance in dexibuprofen RS, %;

m_1 - weight of the powder of powdered tablets, mg;

m_0 - weight of the dexibuprofen RS, mg;

$m_{av.tab.}$ - average weight of tablet, mg.

3.4. Results of quantitative determination of dexibuprofen in tablets

To calculate the quantitative content of dexibuprofen in tablets, the average weight of the tablet was determined in accordance with the requirements of article of the State Pharmacopoeia of Ukraine 2.9.5 "Mass uniformity for a unit of dosed

drug".

The study was conducted on three batches of Zotek-400 (manufactured by Synmedic, India), so the average weight was calculated for each batch. The results are shown in Table 3.2.

The quantitative content of dexibuprofen in the dosage form was determined according to the method described above. The content of the active substance was calculated by the standard method. A sample of dexibuprofen with a nominal active ingredient content of 99.9 % was used as a standard.

Table 3.2

Results of determination of the average weight of tablets

№	tablet weight, mg		
	bantch EDE23003A1	bantch EDE23004A1	bantch EDE23001A1
1.	750,9	754,2	748,9
2.	752,4	753,4	750,3
3.	751,6	754,6	749,6
4.	750,4	751,9	751,2
5.	749,8	752,8	751,0
6.	751,2	755,0	749,8
7.	752,3	752,3	749,3
8.	751,9	754,2	748,6
9.	750,7	752,9	749,8
10.	749,6	752,8	750,2
11.	750,8	754,1	750,6
12.	751,3	753,8	749,1
13.	752,0	752,6	748,9
14.	751,2	753,3	749,3
15.	751,9	755,4	750,3

№	tablet weight, mg		
	bantch EDE23003A1	bantch EDE23004A1	bantch EDE23001A1
16.	753,4	753,8	749,3
17.	749,8	753,6	748,2
18.	752,4	753,2	750,3
19.	750,9	753,9	748,6
20.	752,3	753,7	749,2
Average tablet weight, mg	751,3	753,6	749,6
Standard deviation	1,0	0,9	0,8

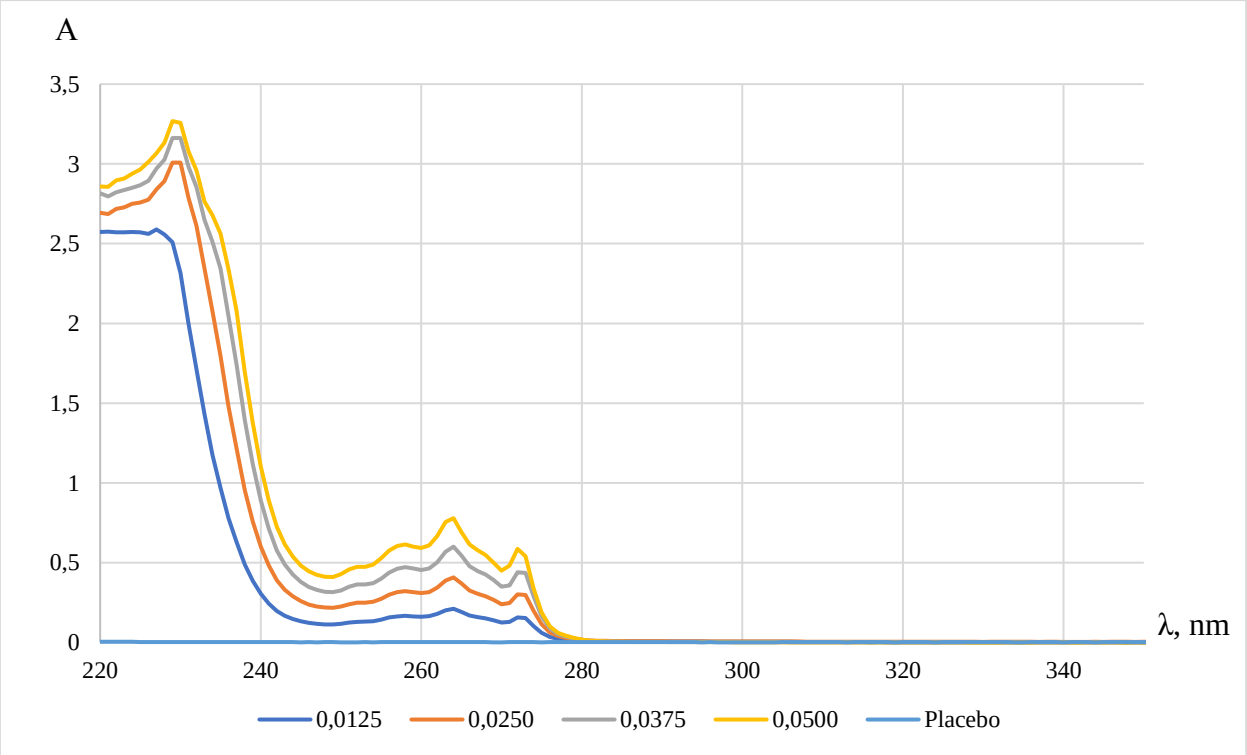


Figure 3.6. UV-spectra of methanol solutions of Zotek tablets and placebo solution

It was established (Figure 3.6) that the absorption of excipients in the tablets in this wavelength range is not more than 0.01, therefore, they do not have a

pronounced effect on the absorption of dexibuprofen solutions when simultaneously present during the analysis.

The results of the quantitative spectrophotometric determination of dexibuprofen in tablets of different batches are given in Table 3.3.

Table 3.3.

Results of quantitative spectrophotometric determination of dexibuprofen in tablets

Bantch	№	Absorption of the solution	Absorption of the standard sample solution	Average tablet weight, mg	Dexibuprofen content, mg
EDE23003A1	1	0,601	0,615	751,3	390,5
	2	0,603			391,8
	3	0,602			391,2
	4	0,601			390,5
	5	0,600			389,9
	6	0,603			391,8
EDE23004A1	1	0,633	0,615	753,6	412,6
	2	0,634			413,3
	3	0,634			413,3
	4	0,631			411,3
	5	0,633			412,6
	6	0,633			412,6
EDE23001A1	1	0,623	0,616	749,6	404,9
	2	0,625			406,2
	3	0,624			405,5
	4	0,623			404,9
	5	0,624			405,5
	6	0,623			404,9

At least six determinations were performed for each series of Zotek®-400, the results were subjected to statistical processing in accordance with the requirements of the State Pharmacopoeia of Ukraine, general article "5.3.N.1. Statistical analysis of chemical experiment results[N]":

Number of degrees of freedom:

$$\nu = n-1$$

The average value of the sample:

$$\bar{x} = \frac{\sum_i^n xi}{n}$$

Dispersion:

$$S^2 = \frac{\sum_i^n xi - n\,\bar{x}^2}{\nu}$$

Standard deviation:

$$S = \sqrt{s^2}$$

Relative average deviation:

$$S_r = \frac{s}{\bar{x}}$$

Relative standard deviation:

$$RSD = S_r \cdot 100\% ;$$

Standard deviation of the average result:

$$S\bar{x} = \frac{s}{\sqrt{n}}$$

Relative standard deviation of the average result:

$$S_{\bar{x},r} = \frac{S\bar{x}}{\bar{x}}$$

Relative standard deviation of the average result, in percent:

$$RSD\bar{x} = S_{\bar{x},r} \cdot 100\%$$

Limit values of the confidence interval of a single measurement result:

$$Xi \pm \Delta X = x_i \pm t(P_2; \nu) \cdot s = x_i \pm t(95\%, 5) \cdot s$$

Limit values of the confidence interval of the mean result:

$$\bar{X}_i \pm \Delta X = \bar{x} \pm \frac{t(P2;\nu)*s}{\sqrt{6}}$$

The relative uncertainty of the average result:

$$\bar{\varepsilon} = \frac{\bar{X}_{i \pm \Delta X}}{\bar{X}} \cdot 100\%$$

The relative uncertainty of a particular definition:

$$\varepsilon = \frac{Xi \pm \Delta X}{\bar{X}} \cdot 100\%$$

The metrological characteristics of the mean result of the spectrophotometric method for the quantitative determination of dexibuprofen in tablets are given in Table 3.4.

Table 3.4.

Metrological characteristics of the mean result of the spectrophotometric method for the quantitative determination of dexibuprofen in tablets

X	$\bar{X}$	ν	X – $\bar{X}$	S^2	S	Sx	ΔX	Δ$\bar{X}$	$\bar{\varepsilon}$	ε
Bantch EDE23003A1										
390,5	390,9	5	-0,4332	0,6192	0,7869	0,3212	0,6462	0,2638	0,07	0,17
391,8			0,8663							
391,2			0,2166							
390,5			-0,4332							
389,9			-1,0829							
391,8			0,8663							
Bantch EDE23004A1										
412,6	412,6	5	0,0000	0,5099	0,7140	0,2915	0,5864	0,2394	0,06	0,14
413,3			0,6518							
413,3			0,6518							

X	$\overline{X}$	ν	$X - \overline{X}$	S^2	S	Sx	ΔX	$\Delta\overline{X}$	$\overline{\varepsilon}$	ε
411,3			-1,3037							
412,6			0,0000							
412,6			0,0000							
Bantch EDE23001A1										
404,9	405,3	5	-0,4332	0,2815	0,5306	0,2166	0,4357	0,1779	0,04	0,11
406,2			0,8665							
405,5			0,2166							
404,9			-0,4332							
405,5			0,2166							
404,9			-0,4332							

The assay was found to be in good agreement with the declared active substance content of the tablets on the label.

In accordance with ICH guidelines, the accuracy was assessed by the standard addition method and the percentage recovery was found to be in the range of 98 to 99. This indicates that there is no interference from excipients in the tablet formulation. Therefore, the proposed spectrophotometric method can be successfully used for the estimation of dexibuprofen in the routine analysis of finished pharmaceuticals.

3.5. Calculation of greenness of the proposed method

Although there are many methods for determining the green nature of an analytical procedure [38], only the "AGREE methodology" [39] uses all 12 principles of green analytical chemistry, including:

1. Prevention of waste generation: Designing a chemical synthesis in such a way that waste is avoided. Do not leave any waste for disposal or burial.

2. Maximising the aggregation of constituent parts: Designing a synthesis so that the final product contains the maximum ratio of starting materials. With minimal or no waste.

3. Development of less hazardous chemical syntheses: Using and generating substances with minimal or no toxicity to humans or the environment.

4. Design of safe chemicals and products: The design of chemical products that are fully effective but have little or no toxicity.

5. Use safe solvents and reaction conditions: Do not use solvents or other auxiliary chemicals. If you must use these chemicals, use the safest ones available.

6. Increase energy efficiency: Run chemical reactions at room temperature and pressure whenever possible.

7. Use renewable raw materials: Use feedstocks or raw materials that are renewable rather than those that are depletable. Sources of renewable raw materials are often agricultural products or wastes from other processes; sources of non-renewable raw materials are more often fossil fuels (oil, natural gas, coal) or mining.

8. Avoid chemical derivatives: Avoid the use of blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

9. Use catalysts, but not stoichiometric reagents: Minimise waste by using catalytic reactions. Catalysts are effective in small quantities and can perform a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and perform a reaction only once.

10. The design of chemicals and products deteriorates after use: The design of chemical products should be such that they degrade to harmless substances after use, and do not accumulate in the environment.

11. Real-time analysis to prevent contamination: Incorporate real-time monitoring and control during synthesis to minimise or eliminate the formation of by-products.

12. Minimising the potential for accidents: The design of chemicals and their physical forms (solid, liquid or gas) to minimise the potential for chemical accidents, including explosions, fires and releases to the environment.

Therefore, the sustainability of the current method was assessed using the AGREE procedure. In figure 3.7 shows a graphical representation of the AGREE report and the AGREE score for each green chemistry principle.

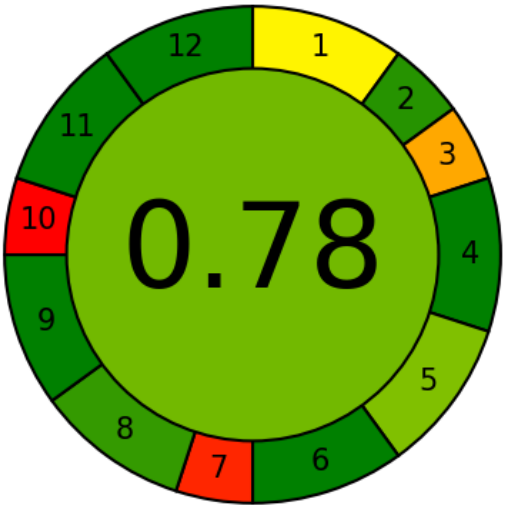


Figure 3.7. AGREE analytical scale for the determination of dexibiprofen by UV-spectrophotometry

As can be seen from the figure 3.7, the method belongs to the green category in terms of environmental friendliness. Due to the fact that the method uses methanol as a solvent, points 7 and 10 demonstrate a high risk of environmental pollution.

To summarise, the selected method of UV absorption spectrophotometry for the determination of dexibuprofen in tablet formulations is environmentally friendly and complies with ISO environmental standards.

Conclusion to Chapter III

1. The conditions for the spectrophotometric determination of dexibuprofen were selected, the analytical wavelength and the optimal concentration

of the active substance were determined, and it was found that under these conditions the solutions under study were stable for 1 hour.

2. A method for the quantitative determination of dexibuprofen by UV absorption spectrophotometry was developed, which is available and can be used for quality control of dexibuprofen tablet medicines.

3. It is possible to identify the compound in the substance and the finished drug product by the maximum light absorption of methanol solutions at wavelengths of 258 nm, 264 nm and 272 nm, which are analytical and can be used for the identification of the compound.

4. For the quantitative determination of dexibuprofen, 258 nm was chosen as the analytical wavelength, at which the methanolic solutions of the sample under study obey the Bouguer-Lambert-Behr law in the concentration range from 0.003 mg/ml to 0.050 mg/ml.

5. The obtained results of the quantitative determination of dexibuprofen in tablets are reliable and metrologically certified.

6. The calculated environmental friendliness of the proposed method for dexibuprofen in the substance and finished drug products in the form of tablets is 0.78, which indicates that the method is green and can be used in routine analysis without harming the environment.

GENERAL CONCLUSION

1. A literature review was carried out on the advantages of using pure stereoisomers in pharmaceutical practice, as well as the peculiarities of their synthesis and purification.

2. The advantages of dexibuprofen over its precursor, ibuprofen, as well as the peculiarities of pharmacological action, metabolic pathways and indications for use were considered.

3. The paper presents the physicochemical properties of dexibuprofen, the method of preparation and modern methods of analysis of dexibuprofen.

4. A method for the quantitative determination of dexibuprofen by ultraviolet absorption spectrophotometry has been developed, which is available and can be used for quality control of dexibuprofen tablet formulations.

5. It is possible to identify the compound in the substance and the finished drug product by the maximum light absorption of methanol solutions at wavelengths of 258 nm, 264 nm and 272 nm, which are analytical and can be used for the identification of the compound.

6. For the quantitative assessment of dexibuprofen, 258 nm was chosen as the analytical wavelength, at which the methanolic solutions of the sample under study obey the Bouguer-Lambert-Behr law in the concentration range from 0.003 to 0.050 mg/ml.

7. The obtained results of the quantitative determination of dexibuprofen in tablets are reliable and metrologically certified.

8. The calculated environmental friendliness demonstrates the greenness of the developed spectrophotometric method for the determination of dexibuprofen in substances and medicinal products in the form of tablets, which proves the compliance of the method with ISO environmental standards and allows us to recommend the introduction of the investigated method into monographs and regulatory documents.

LIST OF REFERENCES

1. A systematic review of NSAIDs treatment for acute pancreatitis in animal studies and clinical trials / D. Wu et al. *Clin. Res. Hepatol. Gastroenterol.* 2020. № 1. P. 1–18.

2. Brater D. C. Clinical Pharmacology of NSAIDs. *Clin. Pharmacol.* 1988. №128. P. 1121–1132.

3. Rainsford K. D. Ibuprofen: Pharmacology, efficacy and safety. *Inflammopharmacology.* 2009. № 17. P. 275–342.

4. Effect of binary solid lipid matrix of wax and triglyceride on lipid crystallinity, drug-lipid interaction and drug release of ibuprofen-loaded solid lipid nanoparticles (SLN) for dermal delivery / T. Chantaburanan et al. *J. Colloid Interface Sci.* 2017. № 504. P. 247–256.

5. Dexibuprofen: Statistical assessment of drug release kinetics and investigative quality perspective / A.M. Hanif et al. *Pak. J. Pharm. Sci.* 2018. № 31. P. 2157–2162.

6. Phleps W. Overview on clinical data of dexibuprofen. *Clin. Rheumatol.* 2001. № 20. P. S15–S21.

7. Azhar D. K., Kaushik R. Nanosponges: A Newer Approach for Novel Drug Delivery. 2017. № 3. P. 1-11.

8. Wsol V., Skalova L., Szotakova B. Chiral inversion of drugs: Coincidence or principle? *Curr. Drug Metab.* 2004. № 5. P. 517–533.

9. Mlachkova A, Dosseva-Panova V. Effectiveness of NSAIDs for pain management in periodontal surgery. *J of IMAB.* 2023. № 29(1). P. 4757-4762.

10. Progress in Lipid Research a -Methylacyl-CoA racemase (AMACR): Metabolic enzyme, drug metabolizer and cancer marker P504S / M.D. Lloyd et al. *Prog. Lipid Res.* 2013. № 52. P. 220–230.

11. Comparison of the efficacy and tolerability of dexibuprofen and celecoxib in the treatment of osteoarthritis of the hip / R. Hawel et al. *Int. J. Clin. Pharmacol. Ther.* 2003. № 41. P. 153–164.

12. Gliszczynska A, Sanchez-Lopez E. Dexibuprofen Therapeutic Advances: Prodrugs and Nanotechnological Formulations. *Pharmaceutics*. 2021. № 13(3). P. 414.

13. Apsen Farmaceutica S.A. Phase I Study to Evaluate the Safety of Dexibuprofen 300 mg Under Fasting and Fed Conditions. URL: https://clinicaltrials.gov/ct2/show/NCT02956512 (Date of access: 20.01.2024).

14. Gebro Pharma GmbH Dexibuprofen Powder for Oral Suspension. URL: https://www.gebro.com/en/produkte/seractil-akut-400-mg-powder-for-oral-suspension/ (Date of access: 20.01.2024).

15. Navigating the human gastrointestinal tract for oral drug delivery: Uncharted waters and new frontiers / M. Koziolek et al. *Adv. Drug Deliv. Rev.* 2016. № 101. P. 75–88.

16. PharmGKB summary: ibuprofen pathways / L. L. Mazaleuskaya et al. *Pharmacogenet Genomics*. 2015. № 25(2). P. 96-106.

17. Interpreting the Benefit and Risk Data in Between-Drug Comparisons: Illustration of the Challenges Using the Example of Mefenamic Acid versus Ibuprofen / A. Farkouh et al. *Pharmaceutics*. 2022. № 14(10). P. 2240.

18. Kaehler S. T., Phleps W., Hesse E. Dexibuprofen: pharmacology, therapeutic uses and safety. *Inflammopharmacology*. 2003. Vol. 11. Iss. 4–6. P. 371–383.

19. Derry S., Best J., Moore R. A. Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults. *Cochrane Database Syst Rev*. 2013. № 2013(10). P. CD007550.

20. Comparison of the bioavailability of dexibuprofen administered alone or as part of racemic ibuprofen / B. Gabard et al. *European journal of clinical pharmacology*. 1995. Vol. 48. Iss. 6. P. 505–511.

21. Aggregation behavior of ibuprofen, cholic acid and dodecylphosphocholine micelles / P. Prakash et al. *Biochim Biophys Acta*. 2012. № 1818(12). P. 3040-3047.

22. Phleps W. Overview on clinical data of dexibuprofen. *Clin Rheumatol*. 2001. Suppl 1. P. S15-21.

23. Efficacy and Safety of NSAIDs in Infants: A Comprehensive Review of the Literature of the Past 20 Years / V. C. Ziesenitz et al. *Paediatr Drugs*. 2022. № 24(6). P. 603-655.

24. Головні болі при патологічних процесах в області шиї / Н. К. Свиридова та ін. *East European Journal Of Neurology*. 2015. № 6 (06). С. 23-28.

25. Saffoon N., Jhanker Y. M., Huda N. H. Dissolution profile of ibuprofen solid dispersion prepared with cellulosic polymers and sugar by fusion method. *Stamford journal of pharmaceutical science*. 2011. № 4(1). P. 31-37

26. Asymmetric synthesis of (S)-ibuprofen by esterification with amides of (S)-lactic acid as chiral auxiliaries. Experimental and theoretical results / A. Ammazzalorso et al. Tetrahedron Lett. 2002. Vol. 43 (24). P. 4325-4328.

27. Pumera M., Jelinek I., Indrich I. β-Cyclodextrin-modified monolithic stationary phases for capillary electrochromatography and nano-HPLC chiral analysis of ephedrine and ibuprofen. *J. Liq. Chromatogr. and Relat. Thechnol*. 2012. Vol. 25. № 16. P. 2473-2484

28. Monitoring of the Optical Purity for Dexibuprofen by HPLC / J. Ryoo et al. *Journal of the Korean Chemical Society*. 2015. № 49. P. 283-289.

29. UV spectrophotometric estimation of dexibuprofen in bulk drug and its pharmaceutical formulation / G. Sukumaran et al. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 2011. № 2. P. 885-890.

30. Державна Фармакопея України / ДП «Український науковий фармакопейний центр якості лікарських засобів». 2–ге вид. Харків : ДП

«Український науковий фармакопейний центр якості лікарських засобів», 2015. Т. 1. 1128 с.

31. Бондаренко Н. Ю., Блажеєвський М. Є. Кількісне визначення ібупрофену методом хемілюмінесценції. *Управління, економіка та забезпечення якості в фармації.* 2017. № 1 (49). С. 6-10

32. Spectrophotometric and spectrofluorometric methods for the determination of non-steroidal anti-inflammatory drugs: A review / A. A. Gouda et al. *Arabian Journal of Chemistry*. 2013. Vol. 6. № 2. P. 145-163.

33. Detection of point mutations by capillary electrophoresis in liquid polymers in temporal thermalgradients / C. Gelfi et al. *Electrophoresis*. 2014. Vol. 15. P. 1506-1511.

34. Damiani P. C., Bearzotti M., Cabezon M. A. Spectrofluometric determination of ibuprophen in pharmaceutical formulations. *J. Pharm. and Biomed. Anal*. 2011. № 3. P. 679-683.

35. Dubey N., Jain D., Jadhawani S. Stability-indicating HPTLC method for simultaneous estimation of famotidine, paracetamol, and ibuprofen in combined tablet dosage forms. *Journal of Planar Chromatography*. 2012. № 25(2). P. 162–167.

36. The European Pharmacopoeia, 10th ed., European Directorate for the Quality of Medicines & HealthCare of the Council of Europe, Strasbourg 2022.

37. The United States Pharmacopoeia, 41 - NF 36, The United States Pharmacopeial Convention, Rockville 2018.

38. Method Development and Validation for Estimation of related Substances in Tilorone Dihydrochloride using RP-HPLC / M. Z. Baktiyar et al. *Research Journal of Pharmacy and Technology*. 2021. № 14 (6). P. 3319–3324.

39. Analytical Eco-Scale for assessing the greenness of analytical procedures / A. Gałuszka et al. *TrAC Trends in Analytical Chemistry*. 2021. № 37. P. 61–72.