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METHODOLOGICAL ASPECTS OF PHARMACEUTICAL ANALYSIS TEACHING IN THE CONTEXT OF STUDYING THE PHARMACEUTICAL CHEMISTRY FOR FOREIGN STUDENTS

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МЕТОДИЧНІ АСПЕКТИ ВИКЛАДАННЯ ФАРМАЦЕВТИЧНОГО АНАЛІЗУ В КОНТЕКСТІ ВИВЧЕННЯ ФАРМАЦЕВТИЧНОЇ ХІМІЇ ІНОЗЕМНИМ СТУДЕНТАМ

Abstract. The article adduces the ways to solve the main problems faced by teachers working with foreign students in teaching pharmaceutical analysis in the context of studying the discipline of Pharmaceutical Chemistry; analyzes the main issues that can affect the performance of the teaching of foreign students.

The research is based on the study of materials obtained from open sources of information and authors' own experience. The article presents modern technologies of teaching and testing of foreign students on Pharmaceutical Chemistry, approved at the Department of Pharmaceutical Chemistry.

Since the quality of the drug is laid down at the stage of pharmaceutical development, the student must clearly know the elements of pharmaceutical development and pharmaceutical analysis. The purpose of pharmaceutical analysis is to: learn general methods of analysis of substances of medicinal substances and to determine their qualities in appearance, solubility and reaction of the environment in accordance with the requirements of the State Pharmacopoeia (SPhU); to study and explain the physical and physico-chemical methods of analysis of organic medicinal products; to be able to carry out reactions of identification of substances of medicinal substances by cations and anions in accordance with the requirements of SPhU; to use chemical methods for the identification of medicinal products of organic structure by analytical-functional groups; to determine the physical constants of organic substances for the identification and purification of medicinal products; to use the definition of refractive index and specific rotation of solutions of drugs for their identification and purity; to practice the general requirements of the SPhU for the testing of the maximum content of impurities; to be able to quantify the content of medicinal substances in the substance by different methods; to be able to conduct qualitative and quantitative rapid-analysis of active substances in extemporal dosage forms. Detailed and thorough acquaintance with the basics of the discipline of Pharmaceutical Chemistry, gives the opportunity to more fully master the studied material, realize the scientific and creative potential of students, enrich their knowledge, which will be directly used in their practical activities.

The proposed method allows the teacher to successfully build an educational process, which ultimately positively affects the overall mastering of the course.

Key words: pharmaceutical analysis; pharmaceutical chemistry; Pharmacopoeia.

Анотація. У статті висвітлено шляхи вирішення основних проблем, з якими стикаються викладачі, що працюють зі студентами-іноземцями при викладанні фармацевтичного аналізу в контексті вивчення дисципліни «Фармацевтична хімія». Проаналізовано основні проблеми, які можуть впливати на результативність навчання студентів-іноземців.

Дослідження базується на вивченні матеріалів, отриманих із відкритих джерел інформації та власного досвіду авторів. У статті наведені сучасні технології викладання та тестування іноземних студентів з фармацевтичної хімії, впроваджені на кафедрі фармацевтичної хімії.

Оскільки якість препарату закладається ще на етапі фармацевтичної розробки, студент чітко повинен знати елементи фармацевтичної розробки та фармацевтичного аналізу. Ціллю фармацевтичного аналізу є: засвоїти загальні методи аналізу субстанцій

лікарських речовин та підтвердження їх доброякісності за зовнішнім виглядом, розчинністю та реакцією середовища згідно з вимогами ДФУ; вивчити і пояснювати фізичні та фізико-хімічні методи аналізу органічних лікарських засобів; вміти проводити реакції ідентифікації субстанцій лікарських речовин за катіонним і аніонним складом згідно з вимогами ДФУ; використовувати хімічні методи для ідентифікації лікарських засобів органічної структури за аналітико-функціональними групами; визначати фізичні константи органічних речовин для ідентифікації та встановлення чистоти лікарських засобів; використовувати визначення показника заломлення і питомого обертання розчинів лікарських засобів для їх ідентифікації і встановлення чистоти; практикувати загальні вимоги ДФУ щодо випробувань на граничний вміст домішок; вміти проводити кількісне визначення вмісту лікарських речовин у субстанції різними методами; вміти проводити якісний та кількісний експрес-аналіз діючих речовин в екстемпоральних лікарських засобах. Детальне і ґрунтовне ознайомлення з основами фармацевтичного аналізу в контексті вивчення дисципліни «Фармацевтична хімія» дає можливість більш повно засвоїти матеріал, що вивчається, реалізувати науково-творчий потенціал студентів, збагачує їх знаннями, які безпосередньо будуть використані в їхній практичній діяльності.

Запропонований метод дозволяє викладачеві успішніше будувати освітній процес, що, в кінцевому підсумку, позитивно позначається на загальному засвоєнні курсу.

Ключові слова: фармацевтичний аналіз; фармацевтична хімія; Фармакопея.

Introduction. Pharmaceutical analysis is mainly focussed in drug analyses, in raw materials and pharmaceutical formulations, involving the determination of active pharmaceutical ingredients, impurities, excipients, content uniformity, solubility, dissolution rate and stability. Pharmaceutical analysis is the backbone of the teaching as well as research in the pharmacy education programme since analysis of the raw material as well as the finished product is of prime importance for the safety and efficacy for human consumption. Since the quality of the drug is laid down at the stage of pharmaceutical development, the student must clearly know the elements of pharmaceutical development. Manufacturing authorisations are required by all pharmaceutical manufacturers in the European Union whether the products are sold within or outside of the Union. To do this, it is necessary to rationalize the organization of the entire educational process, to improve the content, forms, methods of teaching and learning activity of students of higher educational institutions [4, 8].

The aim – to find the ways to solve the main problems faced by teachers working with foreign students in teaching pharmaceutical analysis in the context of studying the discipline of Pharmaceutical Chemistry; analyze the main issues that can affect the performance of the teaching of foreign students.

Methods. The research is based on the study of materials obtained from open sources of information and authors' own experience. The article presents modern technologies of teaching and testing of foreign students on "Pharmaceutical analysis" in the context of study of pharmaceutical chemistry, approved at the Department of Pharmaceutical Chemistry.

The aim of the subject of Pharmaceutical Chemistry follows the goals of educational and professional training programs for graduates of Higher Medical Education Institution and is determined by the content of the systematic knowledge and skills that a pharmacist must comprehend. The knowledge that students receive during study the subject is the basis for block of subjects that provide professional and practical training. Pharmaceutical Chemistry as a subject is based on previously studied by the students subjects such as general and inorganic chemistry, organic and bioorganic chemistry, analytical chemistry, biophysics, biology, biological chemistry, normal physiology, pathological physiology, pharmacology, pharmacognosy, drug technology, clinical pharmacy. Syllabus is divided into two content blocks: Pharmaceutical Analysis and Specialty Pharmaceutical Chemistry.

Results. Pharmaceutical chemistry, as a science is based on the general laws of chemical sciences, studies methods of obtaining, the structure, chemical and physical properties of drugs, the relationship between chemical structure and action on the body, methods of quality control and changes occurring during storage.

The purpose of the discipline Pharmaceutical Chemistry is to: provide systematic knowledge about the structure of drugs, methods for their extraction, identification and quantification, physical, chemical properties, chemical factors of pharmacological action, patterns of the relationship structure – biological/ pharmacological activity and metabolic transformation, purity research, application and storage, as well as approaches to the creation of new synthetic drugs and biologically active substances.

The main tasks of the study of the discipline of Pharmaceutical Chemistry are acquisition of skills in the field of providing quality pharmaceutical care to patients, taking into account knowledge about the physical, physico-chemical and chemical properties of drugs, the basic patterns of "structure-activity" dependence, avoidance of possible interaction of drugs in the process their manufacture and application, the establishment of the quality of individual medicines, their multicomponent mixtures and ensuring their proper storage, acquiring the main methods for the

synthesis of drugs or extraction from natural raw materials; in the field of pharmaceutical analysis.

Lectures cover basic theoretical material of particular or more topics of the discipline, reveal the main issues of the relevant chapters of the discipline. Practical classes (seminar classes) envisage a detailed study by the students of some theoretical principles of the subject with the lecturer and the formation of ability and skills to their practical use by a student's individual performance of various tasks and solving computational problems.

Students' individual work involves mastering an educational material, such as an independent study of particular topics of the subject at the time free from mandatory training classes, and provides preparation to all types of control. Educational material of the subject that is envisaged by a curriculum for learning by the students during independent work is submitted for final control along with educational material that was worked up during the classes.

Consultations (individual or group) are conducted to help students to understand and explain complicated issues for self-understanding, to solve complex problems arising during the independent learning of educational material in preparation for the practical trainings, or before exam. Matricula is considered to be passed when the student with full knowledge of the techniques independently, in strict sequence of work, performed practical skills and formulated conclusions competently. During the performing practical skills the lecturer has the right to direct the student who makes small errors and minor mistakes in carrying out the work. Matricula is considered not to be passed when the student knows the actual material, shows ignorance of the techniques, inability of practical skills, makes gross errors in the sequence of work and the formulation of conclusions.

The main purpose of pharmaceutical analysis in the context of study of pharmaceutical chemistry is to learn general methods of analysis of substances of medicinal substances and to determine their qualities in appearance, solubility and reaction of the environment in accordance with the requirements of the State Pharmacopoeia (SPhU); to study and explain the physical and physico-chemical methods of analysis of organic medicinal products; to be able to carry out reactions of identification of substances of medicinal substances by cations and anions in accordance with the requirements of SPhU; to use chemical methods for the identification of medicinal products of organic structure by analytical-functional groups; to determine the physical constants of organic substances for the identification and purification of medicinal products; to use the definition of refractive index and specific rotation of solutions of drugs for their identification and purity; to practice the general requirements of the SPhU for the testing of the maximum content of impurities; to be able to quantify the content of medicinal substances in the substance by different methods; to be able to conduct qualitative and quantitative rapid-analysis of active substances in extemporal dosage forms.

Nowadays the most modern method of pharmaceutical analysis is physico-chemical methods. Drug manufacturing control requires high level and intensive analytical and chemical support of all stages to ensure the drug's quality and safety. The pharmacopeia constitutes a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances, excipients, and dosage forms that is intended to serve as source material for reference or adaptation by anyone wishing to fulfill pharmaceutical requirements. Direct analyses of target compounds are only possible if the wavelength used is not interfered with by other species. Analyses of mixtures of components are possible by means of derivative spectrophotometry, chemometrics or a chemical derivative obtained by reactions like redox, ion pairing, metal ion chelation, azo dye derivatization, Schiff baseformation and charge transfer complex formation.

The most important analytical technique used during the various steps of drug development and manufacturing is the separation technique: High Performance Liquid Chromatography (HPLC). RP-HPLC for pharmaceutical analysis took off in the early 1970s with the introduction of commercially available microparticulate bonded packings. Although it rapidly became the dominant mode of chromatography in the pharmaceutical area, it quickly became apparent that the chromatography of basic compounds was not a straightforward matter. Despite this, RP-HPLC still figures prominently in both literature and pharmacopeia methods.

Drug development starts with the discovery of a molecule with a therapeutic value. This can be done by high throughput screening during which separations by fast or ultra-fast HPLC are performed. At the discovery stage there can be also characterizing synthetic or natural products. Drug metabolism and pharmacokinetics is the step where the candidate compounds for drug are tested for their metabolism and pharmacokinetics. The studies involve use of LC-MS or LC-MS/MS [5–7].

The next stage is the development stage, where HPLC is used to characterize products of the chemical synthesis, by analyzing the active pharmaceutical ingredients, their impurities and/or degradation products generated by accelerated aging. The development of formulation requires also studies of the dissolution properties of solid dosage forms as well as assays of the pharmaceutical formulations. Method for the verification of system's cleanliness during the manufacturing process are developed and used at this stage. All the HPLC methods that have been finalized at the developmental stage are validated and transferred to the manufacturing laboratories for a quality control analysis.

During the last decade parallel synthesis of potential lead compounds, using combinatorial chemistry, has been done. The large numbers of products created by the combinatorial chemistry are then identified by fast LC-MS methods and screened by in-vitro bioassays and/or pharmacological or chemical tests to allow a selection of a few chosen drug candidates.

When the lead compounds are selected, the next steps involve pharmacological studies. Due to its high sensitivity and selectivity, HPLC coupled with tandem mass spectrometry, HPLC-MS/MS, has become the predominant method in bioassays, and pharmacokinetic and metabolic studies. In addition, another new development in this field has been the introduction of column's packing with ultra-fine particles (<2 um) enabling short columns to be used (5 cm or less) and rapid analyses (e.g., 5 min or even less than 1 min) to be carried out by UPLC (ultra performance liquid chromatography).

The support of bioanalytical testing includes quantitation of a target compound in various biological matrices as part of preclinical lead optimization by measurement its adsorption, distribution, metabolism and excretion. The samples are physiological fluids such as plasma, serum, tissue extracts and urine, typically from experimental animals or human subjects. During the last decade conventional HPLC methods using fluorescence or electrochemical detection, following an elaborate sample clean-up, have been replaced by HPLC-MS/MS or UHPLC-MS/MS methodologies. Sample clean-up is simpler and more automated and usually involves protein precipitation and/or solid phase extraction techniques.

The chromatographic method is typically very rapid, gradient or isocratic, using small columns' dimensions, such as 2.1x50 mm or less. A trace of a typically stable daughter ion signal, obtained from the fragmentation of a parent analyte is used for the detection and quantitation. Such a mode is called MRM (multiple reaction monitoring) or SRM (selective reaction monitoring), which is more stable, sensitive and selective than either the fluorescence or electrochemical signal. Samples are usually ordered in 96 microplates for higher throughput and minimum variability of the sample vials. An internal standard is used typically to minimize assay variability, due to the clean-up stage and MS/MS response, which is still less stable than UV response.

All HPLC methods used for the development of pharmaceuticals and for the determination of their quality have to be validated. In cases whereby methods from the Pharmacopoeia's are used, it is not necessary to evaluate their suitability, provided that the analyses are conducted strictly according to the methods' intended use. In most other cases, especially in cases of modification of the drug composition, the scheme of synthesis or the analytical procedure, it is necessary to re-evaluate the suitability of the HPLC method to its new intended use.

The parameters tested throughout the method validation as defined by the ICH, USP and FDA and other health organizations are the following: specificity or selectivity, precision, accuracy, linearity range, limit of detection, limit of quantitation and robustness.

Teachers are constantly working on improving the necessary teaching and methodological support of the discipline, they seek to acquire knowledge, practical skills, contribute to the formation of scientific outlook, moral, aesthetic and other personal qualities, and the education of the team. They also focus on the needs of the student in certain knowledge, skills and abilities, based on further self-education, since the formation of the personality of a specialist does not end in an educational institution; it lasts for a lifetime during practical activity and continuous improvement of professional skills.

In Middle East and Europe postgraduate students can choose speciality Master of Science in Pharmaceutical Analysis. The overall aim of the Master of Science in Pharmaceutical Analysis programme is to provide advanced training in chemical analysis, with a focus on applications in the pharmaceutical sector, providing students with an appropriate skill-set, knowledgebase and practical experience in preparation for a career either in industrial or academic chemical analysis research in a supportive learning environment. The aims and objectives are to prepare the student to

move directly into graduate level employment in the chemical/pharmaceutical industry, or in a non-chemistry related industry; enhance their employability skills including the ability to work in a team, written and oral presentation skills, numeracy and preparation for self-motivated lifelong learning, professional development and service to society; gain appropriate knowledge and subject specific practical skills to permit students to progress to either an academic research degree (PhD) or an industrial research position; provide a practical research training through successful completion of a substantial piece of research in pharmaceutical analysis; undertake research at the forefront of the analytical sciences at an advanced level. The programme is designed to train students in the appropriate skills for them to be able to pursue a career in chemical analysis, either in an academic or industrial context, with particular focus on pharmaceutical analysis. The course is structured in a way that will ensure hands-on experience with the majority of techniques and instrumentation used nowadays in modern analytical laboratories.

In our opinion, we need to put more attention on undergraduate students for learning of pharmaceutical analysis, which will prepare them for MSc (abroad) and PhD in "Pharmaceutical quality control".

Conclusions and Prospects for Research. Integrating the laws and methods of many sciences plays an important role in studying of Pharmaceutical Chemistry to train the students. It is a part of the discipline of Pharmaceutical Chemistry that preserves the quality of medicines, and hence the health of the people. It allows students to systematize knowledge and practical skills and use them in their professional activities.

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