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STUDY OF THERMOGRAVIMETRIC PROFILE OF A MIXTURE OF DICLOFENAC SODIUM AND PARA-AMINOBENZOIC ACID AS A BASIS FOR PHARMACEUTICAL DEVELOPMENT

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In modern conditions, in particular, against the background of an increase in the frequency of traumatic injuries to the organs of vision because of hostilities and the influence of professional factors, the development of new ophthalmic dosage forms is of particular relevance. Combined drugs containing several active pharmaceutical ingredients, in particular diclofenac sodium and para-aminobenzoic acid, are considered promising solutions for the treatment of infectious and inflammatory eye lesions. At the same time, the effectiveness and safety of such combinations directly depend on their physicochemical compatibility, which determines the stability of the finished dosage form.

***The aim of the study** is to investigate the thermal stability and possible physicochemical interactions between diclofenac sodium and para-aminobenzoic acid by derivatographic analysis of individual substances and their mixture in a 1:1 ratio.*

***Materials and methods.** The objects of the study were the pharmaceutical substances diclofenac sodium, para-aminobenzoic acid and a model mixture of the specified active pharmaceutical ingredients. Thermogravimetric analysis was carried out on a Shimadzu DTG-60 device in thermogravimetric analysis and differential thermal analysis modes in the temperature range of 17–250°C with a heating rate of 10°C/min in an air atmosphere.*

***Results.** In the process of thermogravimetric research, it was established that diclofenac sodium is characterized by high thermal stability. Para-aminobenzoic acid showed three stages of thermal destruction, but analysis of the mixture in a 1:1 ratio did not reveal the appearance of new thermal effects or shifts in the degradation profiles.*

***Conclusions.** The results of thermogravimetric analysis indicate the compatibility of diclofenac sodium and para-aminobenzoic acid in terms of thermal characteristics, which confirms the prospects of their simultaneous use*

***Keywords:** derivatography, thermogravimetry, stability, compatibility, thermal decomposition, active pharmaceutical ingredients, diclofenac sodium, para-aminobenzoic acid, thermal analysis*

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1. Introduction

Since the beginning of the full-scale invasion, cases of eye trauma have become more frequent. Even relatively mild mechanical exposure can damage ocular tissues, and the number of patients who need urgent pharmacological support continues to increase. Recent reports indicate that injuries to the organ of vision account for more than 13% of all traumas registered during hostilities. Although military personnel remain the most affected group, similar injuries are increasingly observed among workers in industrial and agricultural sectors who are exposed to dust, chemicals and mechanical irritants daily.

Traumatic injuries are often followed by inflammation and may be complicated by bacterial or fungal infection, which negatively influences treatment outcomes. As a result, the need for ophthalmic preparations combining several pharmacological actions – anti-inflammatory, antibacterial, antifungal and membrane-stabilising – continues to increase [1, 2].

Recent publications show active development of combination ophthalmic agents in countries such as the USA, Italy, Japan, the Republic of Korea and Israel [3]. Our previous research also focused on analytical methods for determining active substances in combination formulations and optimisation of the assay for 1-(β-phenylethyl)-4-amino-1,2,4-triazolium bromide in injectable dosage forms [4–6]. These findings created the basis for further studies on the physicochemical compatibility of potential active components.

Combined ophthalmic formulations are clinically important because they target several pathogenic mechanisms at once, improve therapeutic efficiency and reduce the number of separate dosage forms required. This is especially relevant for patients with chronic eye diseases who require long-term therapy and strict adherence to treatment. [7].

Using a single preparation that contains several active ingredients reduces the overall load on the cornea and conjunctiva compared with applying multiple indi-

vidual medications. Combining pharmacologically complementary components in one dosage form can also provide a synergistic effect, allow less frequent administration and decrease the number of excipients that may irritate ocular tissues.

The use of multi-component ophthalmic formulations remains relevant, as they help increase the safety and convenience of therapy and meet the strict sterility and quality requirements of ocular dosage forms [8, 9].

Diclofenac sodium is a representative of nonsteroidal anti-inflammatory agents with pronounced analgesic effects. Its mechanism is not fully characterised, although it is known that the drug does not act via the pituitary-adrenal system. The main pharmacological effect is associated with inhibition of prostaglandin synthesis through suppression of prostaglandin synthetase activity [10–13].

When used as ophthalmic drops, diclofenac decreases prostaglandin synthetase activity in inflamed ocular tissues without exerting immunosuppressive effects. Clinical data demonstrate that the preparation reduces intraoperative miosis in cataract surgery and alleviates inflammation after various ophthalmic procedures.

In some cases, after operative interventions observed insignificant and transient increase intraocular pressure, even under the condition use of diclofenac sodium. After instillation of 0.1% solution, the drug rapidly penetrates the aqueous humour, where concentrations vary widely. Systemic absorption is minimal, as unchanged diclofenac is typically undetectable in plasma after a single administration [14].

The feasibility of using diclofenac sodium in ophthalmology increases when it is used as part of combination drugs, rather than as monotherapy. This is due to the possibility of combining the anti-inflammatory and analgesic effects of diclofenac with other pharmacological effects, such as antibacterial or anti-edema activity, which is provided by additional components of the composition. Combined use contributes to increased therapeutic efficacy, reduced duration of treatment and reduced risk of postoperative complications, in particular cystoid macular edema and secondary infection. In addition, the synergistic effect of the active ingredients in combined preparations allows for a reduction in the dosage of each of them, which potentially reduces the likelihood of side effects [15].

Special attention in the context of ophthalmological combinations deserves data on para-aminobenzoic acid as a component with pronounced antioxidant potential. Experimental work in animal models has shown its ability to preserve photoreceptor function, decrease oxidative stress markers, and reduce structural retinal damage [16–18].

The development of dosage forms containing more than one active ingredient requires a thorough assessment of the physicochemical compatibility of the active ingredients, as interactions between components during manufacturing or storage can compromise the stability and biological activity of the drug [19, 20]. To identify such risks at an early stage, developers use both computational prediction tools and experimental analytical methods. Among the latter, derivatographic methods play an important role, as they allow for a detailed assessment of the thermal behavior, stability limits, and degradation pathways of individual substances and their mixtures. Thermogravimetric analysis is widely used to characterize the changes in the mass of a sample during controlled heating and serves as a practical method for detecting potential incompatibilities between active pharmaceutical ingredients [21, 22]. This method helps to identify possible intermediate stages and to identify interactions that may occur in a combination drug product. Such information is critical during pharmaceutical development, as thermal instability or incompatibility of the compounds under investigation may lead to loss of biological activity.

The combination of diclofenac sodium and para-aminobenzoic acid is of particular interest in this context, as both substances may undergo physicochemical changes upon heating, which may affect their biological activity and storage. Diclofenac sodium is a well-known non-steroidal anti-inflammatory drug, while para-aminobenzoic acid may serve as a biologically active component that potentiates the pharmacological action of the former. Studying their combined thermal behavior helps to clarify whether interactions occur between them, to determine the temperature limits of stability, and to assess possible risks associated with technological and storage conditions [23].

Although the individual thermal properties of diclofenac sodium and para-aminobenzoic acid have been previously described in the literature, data on their joint behavior remain unexplored. The study of the thermogravimetric profile of their combination may provide new insights into potential interactions and degradation stages, which is important for the development of stable ophthalmic drugs.

The aim of the study. The purpose of this work is to experimentally evaluate the thermogravimetric profile of a mixture of diclofenac sodium and para-aminobenzoic acid, study the physicochemical compatibility between these compounds, and determine the feasibility of using this combination in the development of eye drops with anti-inflammatory, antibacterial, and antifungal effects.

2. Research planning (methodology)

The study of the thermogravimetric behavior of the combination of diclofenac sodium and para-aminobenzoic acid is based on the physico-chemical interactions between the active ingredients and the need to identify possible thermal incompatibilities.

The first stage included the selection of samples for analysis. The individual active pharmaceutical ingredients – diclofenac sodium and para-aminobenzoic acid, as well as their combination in a 1:1 ratio, were studied separately. This stage allowed us to characterize the main thermogravimetric properties of each substance and determine the temperature ranges in which chemical changes can occur.

In the second stage, thermogravimetric analysis was carried out in combination with differential thermal

analysis using a Shimadzu DTG-60 derivatograph (Japan) in the temperature range from 17°C to 250°C. In this study, the sample weight ranged from 12.65 to 21.01 mg, the heating rate was 10°C/min, and α-Al_2O_3 was used as a reference compound [24]. To ensure reproducibility, the same parameters were maintained throughout all measurements, and the analyses were repeated under the same conditions according to the relevant requirements [25].

At the third stage, a comparative study of the obtained derivatograms was carried out in order to identify changes in the thermal behavior of the components in the mixture compared to individual substances. Special attention was paid to temperature intervals where endo- and exothermic effects overlap or change, which may indicate a physicochemical interaction between active pharmaceutical ingredients.

Thus, the research approach allowed us to assess the thermal stability of each component and the mixture as a whole, determine the critical temperatures of the onset of destruction and melting, and record possible changes in heating profiles that may be important for the pharmaceutical development of the combined dosage form.

3. Materials and methods

The active pharmaceutical ingredients of diclofenac sodium, para-aminobenzoic acid and a mixture of diclofenac sodium and para-aminobenzoic acid (1:1) were used as objects of thermogravimetric studies. Thermogravimetric analysis was performed on a derivatograph "Shimadzu DTG-60" (Japan) with a platinum-platinum-rhodium thermocouple when heating samples in aluminum crucibles (temperature range from 17 to 200°C). α-Al_2O_3 was used as a reference substance. The heating rate was 10°C per minute. The mass of the studied samples was from 12,65 mg to 21,01 mg. The derivatograph graphically recorded the obtained data in the form of T, DTA, TGA curves. The T curve on the derivatogram shows the change in temperature, and the TGA curve shows the change in the mass of the sample during the study period. The DTA curve reflects the differentiation of thermal effects, contains information about endothermic and exothermic maxima, and can be used for qualitative assessment of the derivative.

4. Results

First, the obtained derivatographic profiles of individual active pharmaceutical ingredients – diclofenac sodium, para-aminobenzoic acid (Fig. 1, 2) were studied within the temperature range from 17°C to 250°C, which subsequently allowed us to characterize the thermal stability of these substances during heating.

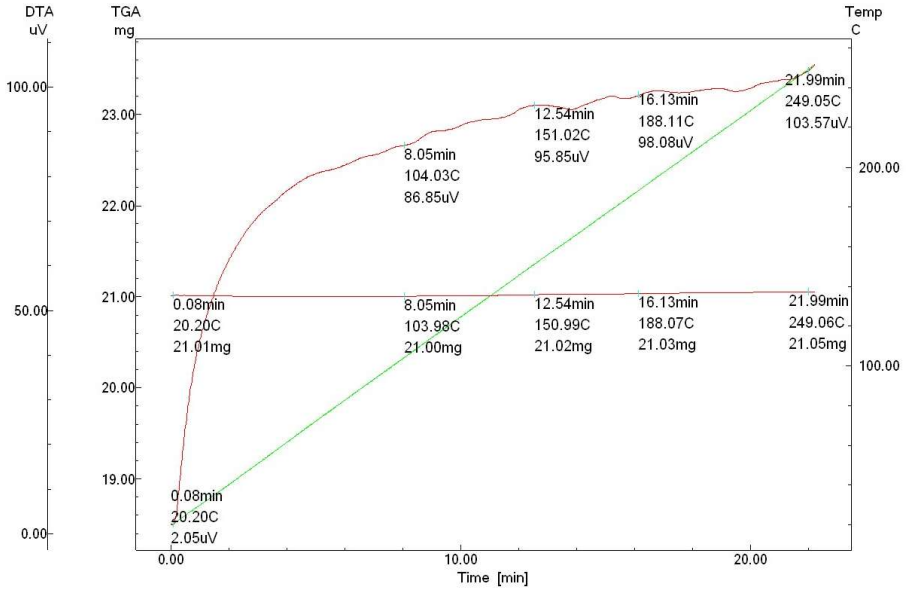

Fig. 1. Derivatogram of diclofenac sodium

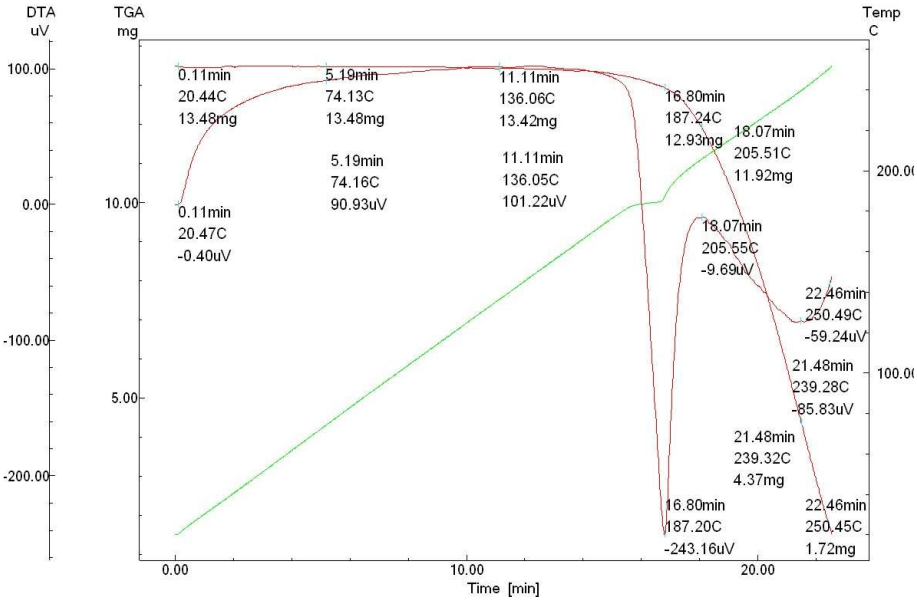

Fig. 2. Derivatogram of para-aminobenzoic acid

In the range of 20–250°C, the diclofenac sodium sample (Fig. 1) does not undergo a noticeable loss of mass: the change is 0.19% of the initial one, which is within the error range of the instrument. The absence of dehydration and evaporation of solvents indicates a high degree of purity of the substance and the absence of water of crystallization. No stage of mass loss was detected, therefore, the beginning of thermal destruction of diclofenac lies above 250°C, which is consistent with the literature data (260–285°C depending on the salt/acid). At temperatures from 70 to 90°C, a low-amplitude endo-

thermic rise was observed, at which traces of adsorbed moisture were probably removed, and already in the range from 150 to 188°C, an endothermic peak was detected, which is associated with the beginning of melting of the substance [15]. The absence of dehydration and mass changes gives reason to consider the substance suitable for technological operations of drying and granulation at temperatures ≤ 120°C without the risk of destruction.

The thermoanalytical profile of para-aminobenzoic acid indicates the presence of three stages. The first stage in the temperature range of 20–136°C is characterized by the stability of the sample mass (the change in mass was less than 0.6%). At the second stage in the temperature range of 135–205°C, the change in the sample mass increased to 11%, which is probably associated with the decarboxylation of the substance. At the third stage in the temperature range of 205–250°C, the change in mass loss significantly increased (less than 75%), which can be characterized as the occurrence of oxidative-thermal destruction. Para-aminobenzoic acid is thermally stable only up to 130°C, further heating leads to an endothermic transition (136°C), after which melting is observed at 187°C, which is accompanied by exothermic decarboxylation and large-scale decomposition to gases and a carbon residue.

Subsequently, an analysis of the derivatogram of a mixture of active pharmaceutical ingredients powders (1:1) was performed - a mixture of diclofenac sodium and para-aminobenzoic acid (Fig. 3).

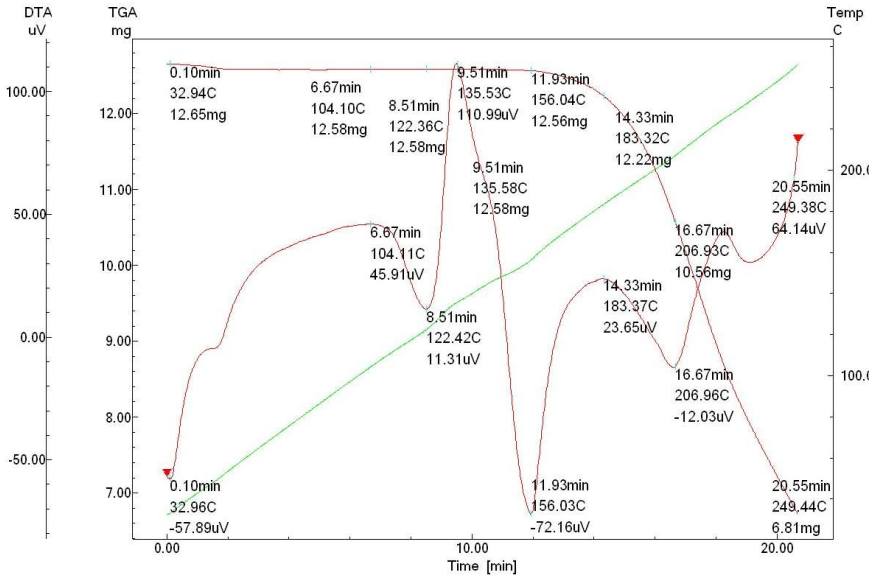

Fig. 3. Derivatogram of a mixture of diclofenac sodium and para-aminobenzoic acid (1:1)

Discussion of the results of the study. The most significant result of the conducted studies is the detection of significant differences in the thermogravimetric profile of the mixture of diclofenac sodium and para-aminobenzoic acid compared to the profiles of each component separately. The thermogravimetric analysis data indicate the presence of changes in the temperature of onset of thermal decomposition and energy characteristics, which may indicate a physicochemical interaction between the components. Similar changes in the thermal behavior of mixtures of pharmaceutical substances are often associated with the formation of intermolecular bonds or partial solvation, which, in turn, affects the stability and bioavailability of the drug.

The results obtained are consistent with the literature, where the study of combinations of NSAIDs with other pharmacologically active substances showed a change in thermal stability and the possibility of improving pharmacokinetic characteristics [1, 3]. In particular, a similar effect was described when combining ibuprofen with antioxidants and when combining naproxen with vitamin E, which led to a shift in the temperature of thermal decomposition towards higher values, increasing the stability of the finished dosage forms. At the same time, in our case, a decrease in the temperature of the onset of mass loss was observed for a mixture of diclofenac sodium and para-aminobenzoic acid, which differs from the results of most studies conducted for similar systems. This may be due to the acid-base properties of para-aminobenzoic acid, which is able to form salts or complexes with diclofenac with lower binding energy than in the original crystalline forms. This feature requires additional studies using IR spectroscopy and powder X-ray diffraction to accurately confirm the mechanism of interaction.

Comparison with international pharmaceutical systems shows that combinations of diclofenac with other active substances are widely used in combination drugs, in particular with misoprostol (Arthrotec®, Pfizer, USA), paracetamol or metamizole, which is aimed at increasing the effectiveness and reducing the side effects of monotherapy. At the same time, the use of diclofenac in combination with para-aminobenzoic acid in ready-made forms is not widespread, which emphasizes the novelty and potential practical value of this study.

The results obtained can be implemented in the development of new combination drugs aimed at reducing the dosage of diclofenac while maintaining or increasing therapeutic efficacy. This will reduce the risks of gastrointestinal complications characteristic of NSAIDs and increase patient compliance with treatment. A promising direction for further research is the study of the pharmacokinetics and pharmacodynamics of such a combination in vivo, as well as determining the optimal ratio of components to ensure maximum stability and therapeutic effect.

5. Discussion

As a result of this study, thermal compatibility between diclofenac sodium and para-aminobenzoic acid

was established. Thermograms of the mixture of the studied substances did not reveal any additional endothermic or exothermic transitions, and did not show any changes in the chemical structure of the individual components. This indicates the absence of physicochemical interactions in the studied temperature range, which is an important aspect for the stability of a promising combined drug. These results confirm previous thermogravimetric and spectroscopic studies of samples containing nonsteroidal anti-inflammatory drugs, where combinations of compounds similarly retained their structural characteristics. Comparison with the literature revealed several parallels and notable differences. For example, the absence of pronounced degradation below 250°C corresponds well to the data presented by [10]. In this study, the onset of decomposition of diclofenac sodium above 260°C is described [10]. In turn, para-aminobenzoic acid showed the characteristic decomposition observed during thermal decarboxylation of this compound [17]. In contrast to combinations containing antioxidants or polyphenolic compounds that slow down the decomposition of compounds with non-steroidal anti-inflammatory activity, the studied mixture showed a slight shift towards lower temperatures [22].

Compared with multicomponent drugs that have been studied internationally, these results confirm the trend towards the development of combined drugs aimed at improving stability and therapeutic efficacy. The mixture of diclofenac sodium and para-aminobenzoic acid remains unexplored, since there are currently no similar drugs with this composition on the pharmaceutical market. This emphasizes the novelty and promising prospects for application in ophthalmology and anti-inflammatory therapy of this study.

Practical significance. The results of this study have significant practical value for the development of new combination drugs. The obtained thermogravimetric data show high stability of the mixture of diclofenac sodium and para-aminobenzoic acid. It also allows you to choose the appropriate technological parameters at the early stages of the development of the dosage form. Such information is very relevant for manufacturers, as it helps to clarify both the composition and the conditions of sterilization and storage of anti-inflammatory drugs. at the same time, high quality and thermal stability of these drugs will be ensured.

The results of this study can also be used in quality control. This will allow early detection of potential thermal incompatibility between active substances and excipients. From the point of view of the study, the methodology presented in this work can serve as a benchmark for studying the thermal behavior and compatibility of other binary or more complex combinations of biologically active compounds.

The results of this study may increase interest in developing therapeutic strategies in which diclofenac sodium can be combined with synergistic compounds to increase its efficacy and reduce adverse reactions. Taken together, the results of this work contribute to the creation of safe, stable and pharmacologically effective drugs and expand the possibilities of pharmacotherapy.

Study limitations. Despite its promising outcomes, the study has several limitations that should be considered. The experiments were performed under controlled laboratory conditions, which do not fully reproduce the range of environmental factors present in industrial manufacturing or long-term storage. The thermogravimetric analysis allows for the evaluation of thermal stability under programmed heating, but it does not consider the influence of humidity, light exposure, or extended storage, which can significantly alter the stability of both diclofenac sodium and para-aminobenzoic acid.

Moreover, the research was limited to a binary system, without including common excipients such as stabilizers that may modify compatibility behavior. Another important limitation is the absence of in vivo or clinical testing of the proposed combination, since the main goal of this work was to establish physicochemical compatibility. Future studies should therefore include pharmacokinetic and safety assessments to confirm the clinical feasibility of the developed approach.

Prospects for further research. Further research should focus on expanding the scope of studies on the influence of different excipients, such as microcrystalline cellulose, polyvinylpyrrolidone or polysorbates, on the thermal and physicochemical behavior of the combination.

Long-term storage tests under stress conditions should be performed to assess the stability of the formulation. Finally, moving from in vitro to in vivo studies would be a logical next step to verify the pharmacodynamic and pharmacokinetic properties of the developed combination and confirm its therapeutic potential in clinical settings.

6. Conclusions

In this study, we studied the thermogravimetric behavior of diclofenac sodium, para-aminobenzoic acid, and their mixture in a 1:1 ratio. The results showed that each substance has its own characteristic thermal profile, which reflects its stability in a certain temperature range. The thermograms of the pure compounds corresponded to the profile of the mixture, indicating the absence of chemical interaction between them during heating. This confirms the compatibility of these two substances at the stage of preliminary technological assessment.

It was also found that technological operations in the production of medicinal products containing these biologically active compounds should not exceed 120°C. Working within this temperature range helps to prevent undesirable chemical changes and preserves the physicochemical properties of both the individual substances and their mixture. This recommendation is important when choosing conditions for sterilization or other processing steps.

Overall, the study confirms that diclofenac sodium and para-aminobenzoic acid remain stable when combined and provides scientific evidence for their potential use in new combination drugs. The results are also

practical for pharmaceutical development, as they help optimize temperature conditions during production, improve the stability of dosage forms and reduce the risk of degradation of biologically active compounds during storage. The novelty of this work lies in establishing the derivatographic characteristics of these substances and confirming their compatibility, which paves the way for further research aimed at creating an effective and safe combination drug in ophthalmology.

Conflict of interest

The authors declare that they have no conflict of interest regarding this study, including financial, personal, academic or other circumstances that could affect the objectivity of the results obtained and the conclusions drawn.

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Data availability

Data confirming the results of this study can be provided by the authors upon reasonable request. This ensures the possibility of independent verification of the results obtained and their further use for scientific and practical purposes while maintaining the confidentiality of the original materials.

Use of artificial intelligence tools

During the preparation of this study, artificial intelligence tools were used. Their application was limited to grammatical checking of Ukrainian and English text without any change in meaning, clarifying a few terms to ensure linguistic accuracy, and detecting minor linguistic inconsistencies such as repetitions or punctuation issues. In addition, artificial intelligence was used to assist in searching for bibliographic sources based on keywords related to thermogravimetric analysis of diclofenac sodium, para-aminobenzoic acid, and compatibility of active pharmaceutical ingredients. For these purposes, the ChatGPT model (OpenAI, GPT-5.1, 2025) was used.

All scientific statements, interpretations, analyses, and conclusions presented in this study are the result of the authors' own work and are based exclusively on experimental findings. Any suggestions obtained from AI, such as grammar-related remarks or lists of potentially relevant sources, were carefully reviewed by the authors for accuracy, relevance, and consistency with experimental data. No AI-generated text was used, directly or indirectly, in the manuscript.

The use of artificial intelligence tools did not influence the research process, data analysis, interpretation of results, or formulation of conclusions. The manuscript fully reflects the authors' own scientific judgment and the outcomes of their experimental work.

Authors' contributions

Liudmila Kucherenko: Conceptualization, Supervision, Project administration, Writing – review & editing; **Dmytro Okolzin:** Investigation, Formal analysis, Writing – original draft, Visualization; **Bohdan Burlaka:** Methodology, Investigation, Validation, Writing – review & editing; **Serhii Borsuk:** Investigation, Resources, Formal analysis, Writing – original draft, Visualization; **Oleksii Bihdan:** Data curation, Validation, Writing – review & editing, Funding acquisition; **Volodymyr Parchenko:** Formal analysis, Validation, Writing – review & editing, Funding acquisition; **Dmytro Skoryna:** Methodology, Data curation, Funding acquisition; **Ivan Pavliuk:** Methodology, Formal analysis, Data curation, Funding acquisition.

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