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The Potentiometric Quantification of Chondroitin Sodium Sulfate Using Ion-Selective Electrodes

Abstract

Chondroitin sodium sulfate is an anionic polysaccharide widely used in pharmaceutical practice as an active ingredient of mono- and multicomponent medicinal products, and its quantitative determination is an essential stage of the quality control. It has been found that the application of potentiometric titration with ion-selective electrodes can increase the accuracy and objectivity of the quantitative analysis, which is of great importance for ensuring the quality and safety of medicines.

The aim of the study was to develop and validate a potentiometric method for the quantitative determination of chondroitin sodium sulfate in the substance and in a combined medicinal product in the form of the sachet powder.

The study objects were chondroitin sodium sulfate substance and a combined medicinal product containing chondroitin sodium sulfate in combination with D-glucosamine sodium sulfate, methylsulfonylmethane, sodium hyaluronate, ascorbic and citric acids, and sorbitol. The conditions of the potentiometric titration with 0.001 M solution of cetylpyridinium chloride were studied using an ion-selective electrode based on cetylpyridinium ionic associates with some lipophilic anions. The titrant was standardized using sodium dodecyl sulfate as a primary standard, as well as the substance itself. The equivalence point was determined from the titration curve and its mathematically processed forms (differential curve, first derivative, and Gran functions). It has been found that the plasticized membrane ion-selective electrodes based on cetylpyridinium associates with dodecyl sulfate and tetraphenylborate anions are characterized by a stable near-Nernstian response in the operating range of cetylpyridinium concentrations of 10^{-3}–10^{-6} mol L^{-1}. The analytical characteristics of the electrodes remained stable for at least 30 consecutive titrations. The selectivity of the reaction between chondroitin sodium sulfate and cetylpyridinium chloride was found, ensuring a clear determination of the equivalence point even in the presence of other mixture components. The influence of pH on the titration results was evaluated; it was shown that in the pH range of 4–8 the shape of titration curves and potential values remained constant, confirming the robustness of the method. The accuracy, precision, linearity (within 80–120 % of the nominal content of the analyte), and the reproducibility of the method were characterized.

It has been experimentally demonstrated that the potentiometric method proposed is accurate, selective, and reproducible for the quantitative determination of chondroitin sodium sulfate both in pure form and in combined medicinal products. The results obtained confirm the analytical suitability of the method developed and the prospects of its implementation in the pharmaceutical analysis practice for the quality control of substances and combined medicinal products of small-scale and industrial production.

Keywords: chondroitin sodium sulfate; potentiometry; quality control; method validation; pharmaceutical analysis; small-scale production

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Потенціометричне кількісне визначення хондроїтин натрію сульфату з використанням іон-селективних електродів

Анотація

Хондроїтин натрію сульфат є аніонним полісахаридом, який широко застосовують у фармацевтичній практиці як активний інгредієнт моно- та багатокомпонентних лікарських засобів і кількісне визначення якого є важливим етапом

контролю якості. З'ясовано, що застосування потенціометричного титрування з іон-селективними електродами дозволяє підвищити точність і об'єктивність кількісного аналізу, що має важливе значення для забезпечення якості та безпеки лікарських засобів.

Метою роботи були розробка та валідація методики кількісного потенціометричного визначення хондроїтин натрію сульфату в субстанції та у складі комбінованого лікарського засобу у формі порошку в саше-пакетах.

Об'єктами дослідження були субстанція хондроїтин натрію сульфату та комбінований лікарський засіб, що містить хондроїтин натрію сульфат у поєднанні з D-глюкозаміну натрію сульфатом, метилсульфонілметаном, натрію гіалуронатом, аскорбіновою та лимонною кислотами, а також сорбітолом. Розглянуто умови потенціометричного титрування 0,001 М розчином цетилпіридинію хлориду з використанням іон-селективного електрода на основі іонних асоціатів цетилпіридинію з деякими ліпофільними аніонами. Стандартизацію титранту здійснювали із застосуванням додецилсульфату натрію як первинного стандарту, а також із використанням субстанції. Точку еквівалентності визначали за кривою титрування та її математично обробленими формами (диференційна крива, перша похідна та функції Грана). З'ясовано, що досліджувані пластифіковані мембранні іон-селективні електроди на основі асоціатів цетилпіридинію з додецилсульфат- та тетрафенілборат-аніонами характеризуються стабільним відгуком, близьким до нернстівського, у робочому діапазоні концентрацій цетилпіридинію 10^{-3}–10^{-6} моль $л^{-1}$. Аналітичні характеристики електродів залишалися стабільними протягом щонайменше 30 послідовних титрувань. Виявлено селективність реакції між хондроїтин натрію сульфатом та цетилпіридинію хлоридом, що забезпечує чітке визначення точки еквівалентності навіть у присутності інших компонентів суміші. Оцінено вплив pH середовища на результати титрування; з'ясовано, що в діапазоні pH 4–8 форма кривих титрування та значення потенціалу залишаються сталими, що підтверджує робастність методики. Схарактеризовано точність, прецизійність, лінійність (у межах 80–120 % від номінального вмісту аналіту) та відтворюваність методики.

Експериментально продемонстровано, що запропонована потенціометрична методика є точною, селективною та відтворюваною для кількісного визначення хондроїтин натрію сульфату як у чистому вигляді, так і у складі комбінованих лікарських засобів. Отримані результати підтверджують аналітичну придатність розробленої методики й перспективність її впровадження в практику фармацевтичного аналізу для контролю якості субстанцій і комбінованих лікарських засобів малосерійного та промислового виробництва.

Ключові слова: хондроїтин натрій сульфат; титрування; контроль якості; валідація методу; фармацевтичний аналіз; малосерійне виробництво

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■ Introduction

Chondroitin sodium sulfate (CS) is a sulfated glycosaminoglycan widely used in pharmaceutical practice as an active pharmaceutical ingredient in both mono- and combination medicinal products for the treatment of degenerative disorders of the musculoskeletal system, particularly osteoarthritis. The pharmacological activity of CS largely depends on its structural characteristics, degree of sulfation, and molecular weight, which necessitates a strict quality control at all stages of the drug production [1].

In recent years, the pharmaceutical market has shown a growing number of combined products containing CS together with glucosamine, methylsulfonylmethane, ascorbic acid, and other biologically active components. Such combinations are aimed at enhancing the anti-inflammatory and chondroprotective effects of these preparations [2]. Therefore, a medicinal product in the form of powder in sachets was selected as the object of this study. Its composition includes glucosamine sodium sulfate (1500 mg), chondroitin sodium sulfate (500 mg), methylsulfonylmethane (400 mg), vitamin C (80 mg), sodium hyaluronate (30 mg), and excipients, such as sorbitol and citric acid [3].

At the same time, the multicomponent composition significantly complicates the pharmaceutical quality control since the presence of polyelectrolytes and surfactants may affect the selectivity and accuracy of the quantitative determination of CS. Recent studies indicate the substantial variability in the qualitative and quantitative composition of chondroitin sodium sulfate, especially in combined medicinal products where impurities of other polysaccharides or excipients may be present [4]. In this regard, the implementation of reliable, selective, and reproducible analytical methods capable of providing an objective quantitative determination of chondroitin sodium

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sulfate in multicomponent systems is an urgent task.

Scientific studies confirm that pharmacopoeial methods may be insufficiently sensitive for the detection and quantitative assessment of combined medicinal products of industrial and small-scale production, which necessitates the development and introduction of new analytical approaches [5].

The ability of chondroitin sodium sulfate to form poorly soluble complexes with cetylpyridinium chloride (CPC) is used for the quantitative analysis of CS in the substance. Indicator-based and photometric titration methods regulated by leading pharmacopoeias consist of two stages: the titration with 4.000 g L^{-1} CPC solution with the visual or instrumental endpoint detection, or the photometric titration with 1.000 g L^{-1} CPC solution [6, 7]. The non-indicator photometric-turbidimetric titration using Mettler-Toledo phototrodes is also widely applied [8, 9].

The disadvantages of these methods include the practical impossibility of performing titration in the presence of certain colored substances and colloidal systems, which usually leads to a significant increase in the analytical uncertainty. For example, it has been reported [10] that this method provides satisfactory results for the determination of CS in chewable tablets only when the effect of the excipient xanthan gum is compensated by adding the same amount to the standard CS solution as contained in the tablets. Similar problems associated with the titration of CS with CPC solutions using the photometric endpoint detection were reported by other authors [11, 12], which partly motivated the present study.

When developing a titrimetric method, it is essential to evaluate validation characteristics, including the method uncertainty, which depends on the titrant standardization approach (primary or secondary) and, in some cases, on the laboratory temperature, burette accuracy, purity of reference standards, and other factors.

In this way, we aimed to develop and validate a potentiometric method for the quantitative determination of chondroitin sodium sulfate in the substance and in a combined medicinal product in the form of the sachet powder.

■ Materials and methods

Reagents and Materials. The study objects included sodium chondroitin sulfate (Bioiberica, S.A.U., R.M. Barcelona, Spain, batch F0932, 100.0% API content, loss on drying – 6.3%) and a novel combined pharmaceutical powder formulation in sachets, containing, in addition to sodium chondroitin sulfate, sodium glucosamine sulfate (Shandong Xiwang Sugar Industry, China, batch XWAC003), ascorbic acid (SD LUWEI Pharmaceutical Co. Ltd, China, batch 201404197), methylsulfonylmethane (Shijiazhuang Jirong Pharmaceutical, China, batch 101-1303006), sodium hyaluronate (Nippon Rica, Japan, batch 5992-143), sorbitol (Evonic Industries, Germany, batch 2111240201), and citric acid monohydrate (Shandong Ensing Industry Co., Ltd, China, batch 3MT2504023).

For titration, cetylpyridinium chloride (CPC) solutions with concentrations of 0.001–0.01 M were used. Sodium dodecyl sulfate (SDS, analytical grade) served as the primary standard for the titrant standardization. All solutions were prepared using purified water.

Equipment. Potentiometric titrations were conducted at 20 ± 5 °C using a cetylpyridinium-selective indicator electrode, with potential readings recorded by a Radelkis OP-208/1 potentiometer equipped with an analog-to-digital converter (ADC ADA-1406, HOLIT DataSystems, Ukraine) under constant stirring on a magnetic stirrer. The measurement scheme: Ag, AgCl/KCl sat./Test solution // Membrane // 10^{-3} M CPC/AgCl, Ag.

Standardization of 0.001 M CPC solution. A 0.2884 g sample of SDS (288.38 g mol^{-1}) was dissolved in distilled water, and the solution was diluted to the volume of 1000 mL in a volumetric flask at 20 °C. Then, 1.0 mL of the resulting 0.01000 M solution or 10.0 mL of the diluted 0.00100 M solution was transferred to a titration cell equipped with the ion-selective electrode, a reference electrode, and a magnetic stirrer. 20–40 mL of water was added, and the solution was titrated with 0.0010 M CPC in 0.5 mL increments, while recording the potential changes of the indicator system. The CPC concentration was calculated as the mean of at least two titrations using the formula:

$$C(\text{CPC}) = C(\text{SDS}) \times \frac{V(\text{SDS})}{V(\text{CPC})} \; [mol\ L^{-1}]$$

Preparation of titration solutions. 0.100 g of sodium chondroitin sulfate or an equivalent amount of the pharmaceutical powder (corresponding to 0.100 g of sodium chondroitin sulfate) was placed in a 100 mL volumetric flask, dissolved in 50 mL of water, and diluted to the volume with water.

The pH of the solution was adjusted to 4.0 using 0.01 M sodium hydroxide. 2.0 mL of this solution was transferred to a titration cell, 20–40 mL of water was added, and the titration was performed potentiometrically with 0.001 M CPC. 1 mL of 0.001 M CPC is equivalent to 0.35 mg of CS.

Potentiometric Titration Conditions. Standard 0.001 M or 0.01 M CPC solutions were added in 0.5 mL increments, and the potential changes (E, mV) were recorded, or the titration was continued until a predetermined potential of the indicator system was reached. Testing the response of the ion-selective electrodes to the cetylpyridinium cation demonstrated the near-Nernstian behavior for a monovalent cation (58 ± ± 3 mV/pC) in the CPC concentration range from 10^{-3} to 10^{-6} mol L^{-1}.

Systematic titration errors were minimized by the primary standardization of the titrant and careful determination of the titration endpoint of the test sample, maintaining a temperature of 20 ± 5 °C and using ISO Class A volumetric glassware [13].

Determination of the CS content. The content of chondroitin sulfate in the substance and pharmaceutical preparation was calculated using the formula:

$$X = \frac{V \cdot K \cdot T \cdot V_{v.fl.} \cdot 100\ (m_{av})}{m_n \cdot V_{pip.}}$$

where: V – is the volume of 0.001 M CPC solution used for titration, mL;
K – is the titration correction factor;
T – is the mass of the analyte equivalent to 1 mL of the titrant of the nominal concentration;
m – is the mass of the sample, g;
m_{av} – is the average sample mass, g.

Data processing. The statistical analysis of the results was performed according to the State Pharmacopoeia of Ukraine (SPhU) 5.3.N.1 "Statistical Analysis of Chemical Experiment Results" [13] using Microsoft Excel. The analysis included calculation of the mean of three determinations, the standard deviation of the mean, and the relative standard deviation. No additional statistical methods were applied as the study had an analytical focus.

■ Results and discussion

The development of a potentiometric titrimetric method for the quantitative determination of CS in a mixture with D-glucosamine sodium sulfate, methylsulfonylmethane, ascorbic acid, sodium hyaluronate, citric acid, and sorbitol involved the following steps:

- the selection of an ion-selective electrode;
- the determination of optimal conditions for the potentiometric titration;
- the standardization of the CPC solution;
- testing the method for the quantitative determination of chondroitin sodium sulfate in the presence of other mixture components;
- the determination of the quantitative content of chondroitin sodium sulfate in the combined medicinal product using the titrimetric method proposed.

Cetylpyridinium chloride belongs to the group of cationic surfactants and is widely used for the potentiometric titration of anionic surfactants. Sodium chondroitin sulfate, due to the presence of carboxyl and sulfate groups in its structure, is a negatively charged polysaccharide. This feature ensures its interaction with CPC cations and provides selectivity of the titrimetric reaction and the determination of the titration end-point using a CPC-selective electrode [14].

The development of the potentiometric titrimetric method for the quantitative determination of sodium chondroitin sulfate in the mixture using the CPC solution began with the selection of an ion-selective electrode. According to the described modified method [15], an ionic associate [16] was obtained by the interaction of aqueous 0.01 M solutions of cetylpyridinium chloride with sodium dodecyl sulfate or sodium tetraphenylborate in the ratio of 1:1. Upon the formation of the corresponding ionic associates, ion-selective membranes were prepared using polyvinyl chloride grade 6602 and Fluka. The PVC electrodes contained approximately 1% of the associate and 73 ± 3% of a plasticizer, which was one of the phthalic acid diesters (octyl, nonyl) or *o*-nitrophenyl octyl ether.

The stability of the prepared ion-selective electrodes based on CPC ionic associates with dodecyl sulfate and tetraphenylborate [17], plasticized with phthalates or *o*-nitrophenyl octyl ether, was tested over 30 consecutive titrations (over the period of 6 months). No significant differences were observed in the titration volume when potentiometrically determining the titration endpoint.

To select the optimal titration conditions, the behavior of potentiometric systems with different electrodes was studied, including the method

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selectivity, the effect of pH, linearity, and reproducibility of the method on the substance, model mixture, medicinal product, and placebo.

During the potentiometric titration of CS with 0.001 M or 0.01 M CPC solutions, a typical titration curve was observed. Two examples for different electrodes are shown in **Figure 1**, presenting one of the differential dependencies. On the titration curve with 0.001 M CPC solution, a titration jump of more than 60 mV was observed. This allows reliable determination of the titration end-point with the minimal influence from the nature of the ion-selective electrode (**Figure 1**).

Due to the asymmetry of titration curves for reactions with stoichiometry different from 1:1 and the frequent heterogeneity of monomer units of natural polyelectrolytes, an important issue arises regarding the correct determination of the equivalence point and the calculation of analytical results. To clarify the uncertainty of such analysis, the behavior of titrimetric systems and methods for processing/calculating titration results were experimentally studied over the period of two years. First of all, the method for the titrant standardization was selected, and the use of sodium dodecyl sulfate as a primary standard proved to be the most appropriate, with control of the results performed using the CS substance standard.

Figure 2 presents the typical data obtained during the titrant standardization using SDS and CS, along with the corresponding methods for processing the experimental data.

As can be seen from the dependences, the titration jump for CS is significantly smaller compared to that for SDS; however, it allows the determination of CS at concentrations in the titrated solution ranging from 0.02 to 10 mg mL^{-1} at the corresponding titrant concentration (with a titer of 0.35–3.50 mg mL^{-1}).

The titrant (CPC) volume corresponding to the equivalence point was determined using various approaches, namely: the titration to a constant potential corresponding to the equivalence point (E_end), processing of EMF dependences f(t) by the Gran method, and the calculation of derivatives (**Figure 2**). It has been found that the most reliable method in terms of selectivity and accuracy is titration to a predetermined E_end value previously determined based on the standardization data and the CS substance titration. Due to the asymmetry of the chondroitin titration curve caused by interaction coefficients differing from unity, this approach makes it possible to obtain reliable results.

During the titrant (CPC) standardization using SDS, any of the listed methods for determining the titration end-point may be applied, which, in contrast to the CS titration, yield practically identical results (**Figure 2***B*). It should be noted that differential processing of curves is sensitive to the titrant portion volume interval ΔV_{CPC} introduced during the titration and, accordingly, may be characterized by higher uncertainty.

The presence of foreign interferents forming more stable/less soluble ionic associates with cetylpyridinium leads, under conventional titration conditions, to positive systematic errors in the determination of chondroitin sulfate. However, when

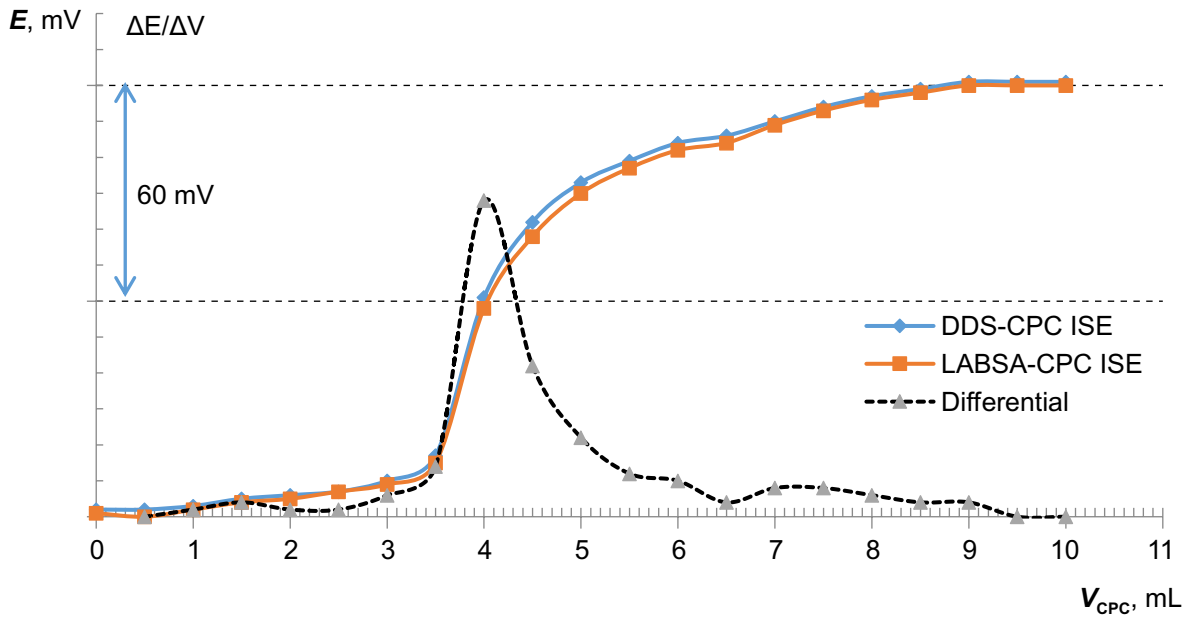

Figure 1. Original (classical) and differential titration curves of the chondroitin sodium sulfate sample titrated with 0.01 M CPC solution using two different ion-selective electrodes

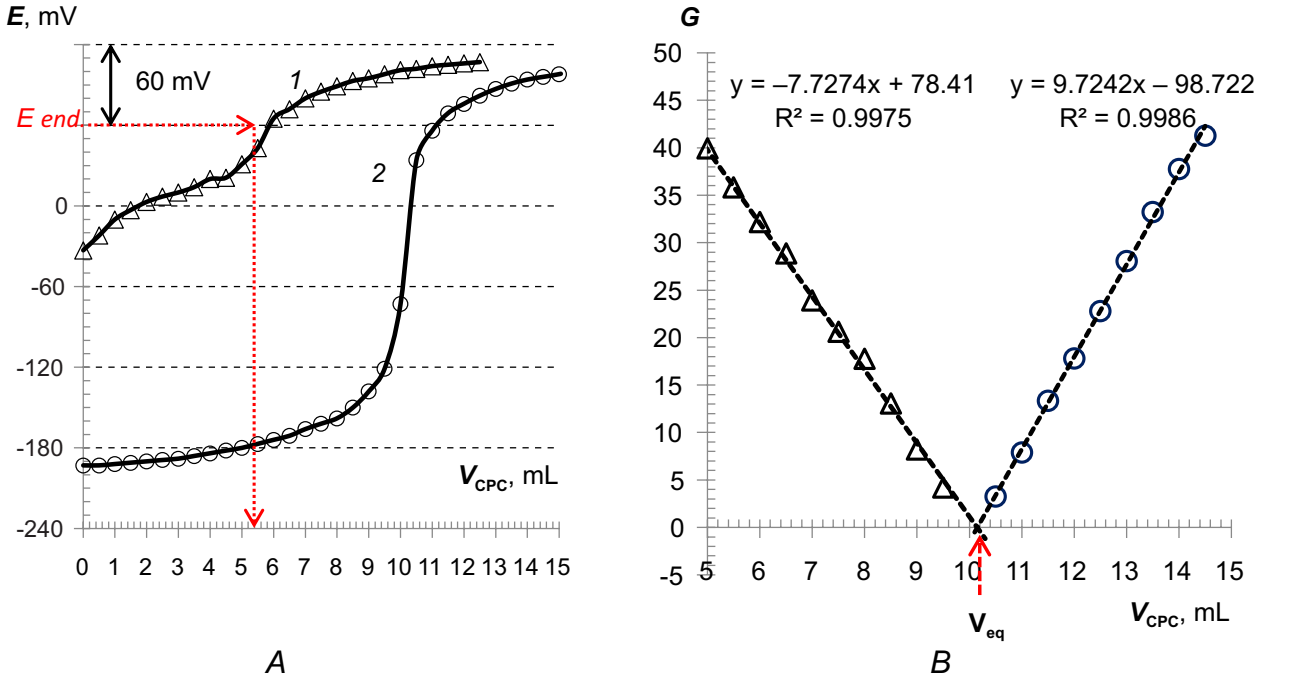

Figure 2. Potentiometric titration curves obtained with 0.001 M CPC solution for the standard SDS solution (2) and the chondroitin sodium sulfate substance solution (1) using a TPhB–CPC electrode (*A*), and processing of the SDS titration curve by the Gran method (*B*): $G = (V_{total} + V_{CPC}) \times 10^{(k \pm E)S^{-1}}$

this effect is taken into account by constructing differential curves, such influences can be partially considered and compensated (**Figure 3**). Nevertheless, it should be taken into account that the differential form indicates the inflection point of the titration curve, which does not coincide with the equivalence point when the titration stoichiometry differs from 1:1. This will play a certain role when titrating minimal amounts of CS.

If the titration is performed in the presence of foreign polyelectrolytes forming less stable/more soluble ionic associates, such as hyaluronate, the systematic error can be eliminated by the titration to a specific potential corresponding to the equivalence point of the chondroitin–cetylpyridinium interaction reaction (**Figure 4**).

Thus, when titrating CS in the presence of foreign interferents, for example, hyaluronic acid, reliable results are obtained only when the

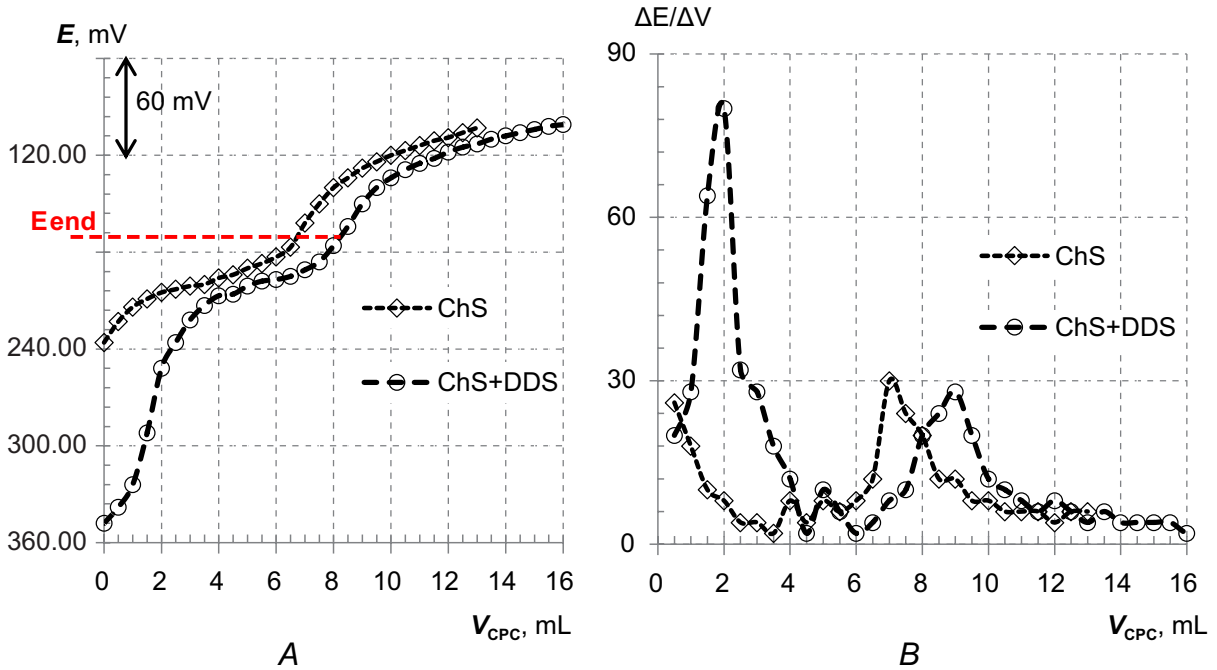

Figure 3. Titration curves obtained with 0.001 M CPC solution: *A*) glucosamine (ChS) and a mixture of glucosamine with sodium dodecyl sulfate (SDS); *B*) corresponding differential dependences

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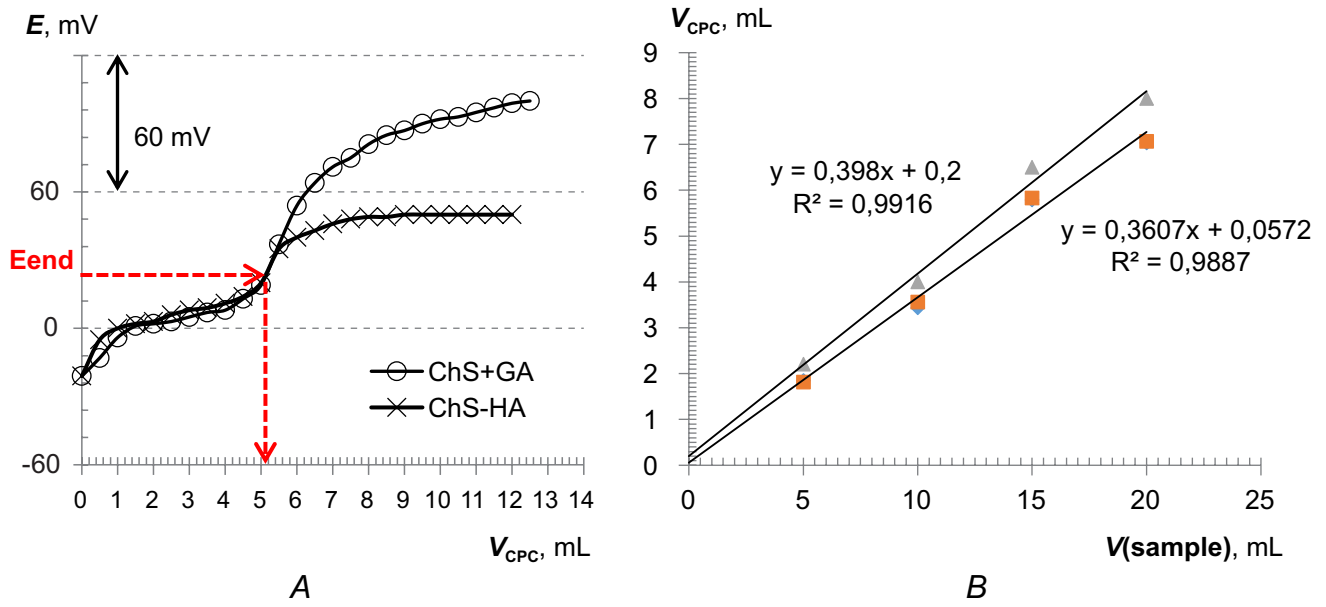

Figure 4. Titration curves of chondroitin sulfate obtained with 0.001 M CPC solution in the presence of an eight-fold excess of glucosamine and, respectively, a ten-fold excess of sodium hyaluronate (*A*), and plots of the titrant volume versus the sample volume using different methods for the end-point determination (*B*)

titration is performed to a constant potential value (E_{end}).

The titration to a constant E_{end} value is convenient for automation of titration using autotitrators. The Gran function applied to the data obtained after the equivalence point does not allow correct results to be obtained in the presence of anionic interferents capable of interacting with CPC to form ionic associates of lower stability/higher solubility compared to CPC–CS associates. Taking into account the stability of CS ionic associates compared to SDS associates, and under satisfactory performance of the ion-selective indicator electrode, the titration end-point potential (E_{end}) can be selected based on the end-point potential of the SDS titration with CPC solutions, which in the case of 0.001 M titrant solution will be 60–70 mV more positive.

The linearity of the method was studied by titrating different sample volumes of the chondroitin sodium sulfate solution with different data processing approaches (**Figure 4***B*). The linearity of the quantitative potentiometric determination of chondroitin sodium sulfate in the mixture was studied within ± 5% acceptance limits relative to the nominal concentration of the active compound in the range from 80% to 120% according to the method, and a calibration plot in normalized coordinates was constructed (**Table 1**) [13].

The study of the dependence of the electroanalytical properties of the ion-selective electrode on the solution acidity showed that the electrode response and the shape of titration curves remained constant within the pH range of 4–8.

Table 1. Validated method parameters

Parameter	Result
Number of determinations	27 (9 × 3 aliquots)
Concentration range	80–120% (80.0–120.0 mg)
a	0.200
b	0.398
r^2	0.9916 Complies
Mean value of Z%	100.09
The lack of statistically significant the systematic error: δ ≤ 1.89	0.5523 ≤ 1.89 Complies
The practical insignificance of the systematic error: δ ≤ 1.0667	0.09 ≤ 1.0667 Complies
The overall conclusion on precision and accuracy	Complies

The study of dependence of the electroanalytical properties of the ion-selective electrode on the medium acidity demonstrated that in the pH range of 4–8, the electrode response and the shape of potentiometric titration curves remained stable. The results obtained indicate the absence of a significant pH effect on the course of the titrimetric reaction, confirming the robustness of the method developed and the possibility of its application over a wide range of analytical conditions.

The results of the quantitative determination of chondroitin sodium sulfate in the substance and in the combined medicinal product are presented in **Table 2**.

It was found that the actual content of the active substance agreed with the declared value. The relative standard deviation (RSD) did not exceed 3.0% in any determination, meeting the

Table 2. The results of the CS determination in the substance and the medicinal product

Test object	Declared content	Found content	SD	RSD	Conclusion
Substance	100.0 %	100.13 %	0.2628	0.26	Complies
Medicinal product	500.0 mg	500.36 mg	1.3106	0.26	Complies

pharmacopoeial requirements for analytical methods. The data obtained confirm the accuracy and practical applicability of the method proposed for the quality control of finished medicinal products.

The approach proposed can be integrated into routine quality control without the use of expensive equipment, which makes it attractive for laboratories of small and medium-sized pharmaceutical enterprises.

■ Conclusions

A potentiometric method for the quantitative determination of chondroitin sodium sulfate using a cetylpyridinium-selective electrode has been developed and validated. The method is characterized by the simple sample preparation and the total analysis time of no more than 15–20 min per sample.

The effect of other active pharmaceutical ingredients and excipients of the medicinal product has been studied, and it has been shown they do not to have a statistically significant effect on the analytical results ($p > 0.05$), confirming the specificity of the method.

The method is characterized by linearity, accuracy, and reproducibility, complying with the pharmacopoeial requirements and ICH recommendations.

The results obtained allow recommending the application of the method developed not only in scientific research, but also in practical activities of large pharmaceutical enterprises and pharmacies engaged in small-scale production, including control of the incoming raw material and finished medicinal products of chondroitin sodium sulfate of both small-scale and industrial manufacture.

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