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ҚАЙЫРЫМДЫЛЫҚ ҚОРЫ
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**«ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫ» РҚБ
«ХАЛЫҚ» ЖҚ**

БАЯНДАМАЛАРЫ

ДОКЛАДЫ

**РОО «НАЦИОНАЛЬНОЙ
АКАДЕМИИ НАУК РЕСПУБЛИКИ КАЗАХСТАН»
ЧФ «ХАЛЫҚ»**

REPORTS

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ЧФ «ХАЛЫҚ»

В 2016 году для развития и улучшения качества жизни казахстанцев был создан частный Благотворительный фонд «Халык». За годы своей деятельности на реализацию благотворительных проектов в областях образования и науки, социальной защиты, культуры, здравоохранения и спорта, Фонд выделил более 45 миллиардов тенге.

Особое внимание Благотворительный фонд «Халык» уделяет образовательным программам, считая это направление одним из ключевых в своей деятельности. Оказывая поддержку отечественному образованию, Фонд вносит свой посильный вклад в развитие качественного образования в Казахстане. Тем самым способствуя росту числа людей, способных менять жизнь в стране к лучшему – профессионалов в различных сферах, потенциальных лидеров и «великих умов». Одной из значимых инициатив фонда «Халык» в образовательной сфере стал проект Ozgeris powered by Halyk Fund – первый в стране бизнес-инкубатор для учащихся 9-11 классов, который помогает развивать необходимые в современном мире предпринимательские навыки. Так, на содействие малому бизнесу школьников было выделено более 200 грантов. Для поддержки талантливых и мотивированных детей Фонд неоднократно выделял гранты на обучение в Международной школе «Мирас» и в Astana IT University, а также помог казахстанским школьникам принять участие в престижном конкурсе «USTEM Robotics» в США. Авторские работы в рамках проекта «Тәлімгер», которому Фонд оказал поддержку, легли в основу учебной программы, учебников и учебно-методических книг по предмету «Основы предпринимательства и бизнеса», преподаваемого в 10-11 классах казахстанских школ и колледжей.

Помимо помощи школьникам, учащимся колледжей и студентам Фонд считает важным внести свой вклад в повышение квалификации педагогов, совершенствование их знаний и навыков, поскольку именно они являются проводниками знаний будущих поколений казахстанцев. При поддержке Фонда «Халык» в южной столице был организован ежегодный городской конкурс педагогов «Almaty Digital Ustaz.

Важной инициативой стал реализуемый проект по обучению основам финансовой грамотности преподавателей из восьми областей Казахстана, что должно оказать существенное влияние на воспитание финансовой грамотности и предпринимательского мышления у нового поколения граждан страны.

Необходимую помощь Фонд «Халык» оказывает и тем, кто особенно остро в ней нуждается. В рамках социальной защиты населения активно проводится работа по поддержке детей, оставшихся без родителей, детей и взрослых из социально уязвимых слоев населения, людей с ограниченными возможностями, а также обеспечению нуждающихся социальным жильем, строительству социально важных объектов, таких как детские сады, детские площадки и физкультурно-оздоровительные комплексы.

В копилку добрых дел Фонда «Халык» можно добавить оказание помощи детскому спорту, куда относится поддержка в развитии детского футбола и карате в нашей стране. Жизненно важную помощь Благотворительный фонд «Халык» оказал нашим соотечественникам во время недавней пандемии COVID-19. Тогда, в разгар тяжелой борьбы с коронавирусной инфекцией Фонд выделил свыше 11 миллиардов тенге на приобретение необходимого медицинского оборудования и дорогостоящих медицинских препаратов, автомобилей скорой медицинской помощи и средств защиты, адресную материальную помощь социально уязвимым слоям населения и денежные выплаты медицинским работникам.

В 2023 году наряду с другими проектами, нацеленными на повышение благосостояния казахстанских граждан Фонд решил уделить особое внимание науке, поскольку она является частью общественной культуры, а уровень ее развития определяет уровень развития государства.

Поддержка Фондом выпуска журналов Национальной Академии наук Республики Казахстан, которые входят в международные фонды Scopus и Wos и в которых публикуются статьи отечественных ученых, докторантов и магистрантов, а также научных сотрудников высших учебных заведений и научно-исследовательских институтов нашей страны является не менее значимым вкладом Фонда в развитие казахстанского общества.

С уважением,
Благотворительный Фонд «Халык»!

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
БАЯНДАМАЛАРЫ
2024 • 2

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РЕДАКЦИЯЛЫҚ АЛҚА:

РАМАЗАНОВ Тілекқабыл Сәбитұлы, (бас редактордың орынбасары), физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі (Алматы, Қазақстан), H = 26

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САНГ-СУ Квак, PhD (биохимия, агрохимия), профессор, Корей биоғылым және биотехнология ғылыми-зерттеу институты (KRIBB), өсімдіктердің инженерлік жүйелері ғылыми-зерттеу орталығының бас ғылыми қызметкері, (Дэчон, Корея), H = 34

БЕРСІМБАЕВ Рахметқажы Ескендірұлы, биология ғылымдарының докторы, профессор, ҚР ҰҒА академигі, Еуразия ұлттық университеті. Л.Н. Гумилев (Нұр-Сұлтан, Қазақстан), H = 12

ӘБИЕВ Руфат, техника ғылымдарының докторы (биохимия), профессор, Санкт-Петербург мемлекеттік технологиялық институты «Химиялық және биотехнологиялық аппаратураны оңтайландыру» кафедрасының меңгерушісі, (Санкт-Петербург, Ресей), H = 14

ЛОКШИН Вячеслав Нотанович, медицина ғылымдарының докторы, профессор, ҚР ҰҒА академигі, «PERSONA» халықаралық клиникалық репродуктология орталығының директоры (Алматы, Қазақстан), H = 8

СЕМЕНОВ Владимир Григорьевич, биология ғылымдарының докторы, профессор, Чуваш республикасының еңбек сіңірген ғылым қайраткері, «Чуваш мемлекеттік аграрлық университеті» Федералдық мемлекеттік бюджеттік жоғары білім беру мекемесі Акушерлік және терапия кафедрасының меңгерушісі, (Чебоксары, Ресей), H = 23

ФАРУК Асана Дар, Хамдар аль-Маджида Хамдард университетінің шығыс медицина факультеті, Шығыс медицинасы колледжінің профессоры, (Карачи, Пәкістан), H = 21

ЩЕПЕТКИН Игорь Александрович, медицина ғылымдарының докторы, Монтана штаты университетінің профессоры (Монтана, АҚШ), H = 27

КАЛАНДРА Пьетро, PhD (физика), наноқұрылымды материалдарды зерттеу институтының профессоры (Рим, Италия), H = 26

МАЛЬМ Анна, фармацевтика ғылымдарының докторы, профессор, Люблин медицина университетінің фармацевтика факультетінің деканы (Люблин, Польша), H = 22

БАЙМҰҚАНОВ Дастан Асылбекұлы, ауыл шаруашылығы ғылымдарының докторы, ҚР ҰҒА корреспондент мүшесі, "Мал шаруашылығы және ветеринария ғылыми-өндірістік орталығы" ЖШС мал шаруашылығы және ветеринарлық медицина департаментінің бас ғылыми қызметкері (Нұр-Сұлтан, Қазақстан), H=1

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ҚАЛИМОЛДАЕВ Мақсат Нұрәділұлы, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі (Алматы, Қазақстан), H = 7

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QUEVEDO Hemando, профессор, Ядролық ғылымдар институты (Мехико, Мексика), H = 28

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ТАКИБАЕВ Нұрғали Жабағаұлы, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі, әл-Фараби атындағы Қазақ ұлттық университеті (Алматы, Қазақстан), H = 5

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ДАВЛЕТОВ Асқар Ербуланович, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі, әл-Фараби атындағы Қазақ ұлттық университеті (Алматы, Қазақстан), H = 12

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ДОКЛАДЫ 2024 •2
НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК РЕСПУБЛИКИ КАЗАХСТАН

ГЛАВНЫЙ РЕДАКТОР:

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ЛОКШИН Вячеслав Нотанович, доктор медицинских наук, профессор, академик НАН РК, директор Международного клинического центра репродуктологии «PERSONA» (Алматы, Казахстан), H = 8

СЕМЕНОВ Владимир Григорьевич, доктор биологических наук, профессор, заслуженный деятель науки Чувашской Республики, заведующий кафедрой морфологии, акушерства и терапии, Федеральное государственное бюджетное образовательное учреждение высшего образования «Чувашский государственный аграрный университет» (Чебоксары, Чувашская Республика, Россия), H = 23

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ЩЕПЕТКИН Игорь Александрович, доктор медицинских наук, профессор Университета штата Монтана (США), H = 27

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БАЙМУКАНОВ Дастанбек Асылбекович, доктор сельскохозяйственных наук, член-корреспондент НАН РК, главный научный сотрудник Департамента животноводства и ветеринарной медицины ТОО «Научно-производственный центр животноводства и ветеринарии» (Нур-Султан, Казахстан), H=1

ТИГИНЯНУ Ион Михайлович, доктор физико-математических наук, академик, президент Академии наук Молдовы, Технический университет Молдовы (Кишинев, Молдова), H = 42

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STUDY OF PHYSICOCHEMICAL EQUILIBRIA IN API SOLUTIONS AT DIFFERENT DILUTIONS

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Abstract. The formulation of new drugs that exert a wide spectrum of activity is a relevant issue. Knowledge of the physicochemical characteristics and structure of the drug is necessary in order to correctly interpret the mechanism of its action and distribution after administration to the body. Finally, the structure and properties of the drug determine both the medicinal form and the method of dosage. In this regard, our work was aimed to study the structure and properties of active pharmaceutical ingredient (API) using a complex of physicochemical methods. According to the results of viscometric studies, the solutions of API were found to be non-Newtonian liquids and the dependence tendency between the temperature increase and solution viscosity decrease was found out, what indicates the occurrence of the decomposition processes, or the existing structures, or associations disaggregation. The data on viscometric studies correlate with the data obtained from calculations of the activation energies of the viscous flow (E_a). Also, the electrical conductivity of API solutions at the temperature of 20–25 °C was studied using the conductometric method. Measurements of the electrical conductivity of API solutions showed that with an increase in the drug content, the values of the specific conductance (χ, mS/cm) rise. This is due to an increase in the quantity of electrically conductive particles in the system, which occurs both due to the concentration of solutions and disaggregation of the micelles.

Keywords: Association, Dynamic viscosity, Specific conductance, potentiometry, redox potential, microscopy

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ӘРТҮРЛІ СҰЙЫЛТУЛАРДАҒЫ АФС ЕРІТІНДІЛЕРІНДЕГІ ФИЗИКА-ХИМИЯЛЫҚ ТЕПЕ-ТЕҢДІКТІ ЗЕРТТЕУ

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Аннотация. Әсер ету спектрі кең жаңа препараттарды жасау өзекті мәселе болып табылады. Денеге енгізгеннен кейін әсер ету механизмін және оның әрекетін дұрыс түсіндіру үшін препараттың физика-химиялық сипаттамалары мен құрылымын білу қажет. Препараттың құрылымы мен қасиеттері, соңында дәрілік форманы да, енгізу әдісін де анықтайды. Осыған байланысты біздің зерттеу жұмысымыздың мақсаты физика-химиялық әдістер кешенін қолдана отырып, активті фармацевтикалық субстанциялардың (АФС) құрылымы мен қасиеттерін зерттеу болды. Вискозиметриялық зерттеулердің нәтижелері бойынша АФС ерітінділерінің ньютондық емес сұйықтар екендігі және температураның жоғарылауымен ерітінділердің тұтқырлығы төмендейтіні анықталды, бұл - құрылымдардың немесе ассоциаттардың ыдырау немесе бөлшектену процестеріне ұшырауын көрсетеді. Вискозиметриялық зерттеулердің деректері мен тұтқыр ағыстың активтену энергиясының (Ea) есептеулерінен алынған мәліметтер сәйкес келеді. Сондай-ақ кондуктометриялық әдіспен 20–25 °C температурада АФС ерітінділерінің электрөткізгіштігі зерттелді. АФС ерітінділерінің электрөткізгіштігін өлшеу, дәрілік заттардың мөлшері артқан сайын меншікті электрөткізгіштік мәндері (χ, mS/cm) жоғарылайтынын көрсетеді. Бұл ерітінділердің концентрациясы есебінен де, мицеллалардың ыдырауынан да пайда болатын жүйедегі электрөткізгіш бөлшектер санының артуына байланысты.

Түйін сөздер: ассоциация, динамикалық тұтқырлық, электр өткізгіштік,

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ИССЛЕДОВАНИЕ ФИЗИКО-ХИМИЧЕСКИХ РАВНОВЕСИЙ В РАСТВОРАХ АФС ПРИ РАЗЛИЧНЫХ РАЗВЕДЕНИЯХ

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Аннотация. Создание новых лекарственных препаратов, которые обладают широким спектром действия является актуальной проблемой. Знание физико-химических характеристик и строения препарата является необходимым для того, чтобы правильно трактовать механизм действия и его поведение после введения в организм. Строение и свойства препарата, в конечном итоге, определяют и лекарственную форму, и способ применения. В связи с этим целью наших исследований явилось изучение при помощи комплекса физико-химических методов строения и свойств активные фармацевтические субстанции (АФС). По результатам вискозиметрических исследований установлено, что растворы АФС являются неньютоновыми жидкостями и было установлено, что с повышением температуры вязкость растворов уменьшается, что свидетельствует о протекании процессов распада или дезагрегации имеющихся структур или ассоциаций. Данные вискозиметрических исследований коррелируют с данными полученных при расчетах энергий активации вязкого течения (E_a). Также кондуктометрическим методом была изучена электропроводность растворов АФС при температуре 20–25 °С. Измерения электропроводности растворов АФС показывают, что с повышением содержания лекарственного препарата значения удельной электропроводности

(χ, mS/cm) растут. Это обусловлено увеличением количества электропроводящих частиц в системе, происходящее как за счет концентрирования растворов, так и за счет дезагрегации мицелл.

Ключевые слова: ассоциация, динамическая вязкость, удельная электропроводность, потенциометрия, окислительно-восстановительный потенциал, микроскопия

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Introduction

Iodine has been used as an antiseptic to prevent and treat a wide range of infections for the long time ago. However, its use has been limited by a number of undesirable factors, such as irritation, sensitization, staining of biological and artificial surfaces, low solubility in water and high vapor pressure. In the early 1950s, the “conquest” of iodine began with the study of its complex formation with certain polymers to form a new class of compounds known as iodophors (Garg et al., 2007). Iodophors are chemical complexes containing a mixture of molecular iodine, iodide ions and a solubilizing agent (Klimaviciute et al., 2012). Natural and synthetic water-soluble polymers and nonionic surfactants are widely used as solubilizing agents. Complexation with polymer carriers increases the solubility of molecular iodine, promotes its prolonged release (Boddie et al.,1997) and reduces the steady-state concentration of free iodine (Kaiho et al., 2014).

Iodine has antimicrobial and antiseptic properties. While antibiotics are localized in a specific location, iodine simultaneously affects all structures of the microbial cell. Iodine binds to proteins, causing their denaturation through several mechanisms, for example, by oxidizing SH groups on cysteine and methionine residues and preventing the formation of hydrogen bonds between the amino groups of arginine and histidine and the phenolic groups of tyrosine. Changes affect the structure and function of microbial cells. In addition, iodine is able to bind to fatty acids via C–C bonds and some nucleotides (adenine, cytosine and guanine), thereby changing the structure of nucleic acids and the entire bacterial cell membrane. Thus, membranes and cytoplasm are rapidly destroyed in cells exposed to iodine (Garg et al., 2007). For example, the effects of the iodophore polyvinylpyrrolidone (PVP)-iodine have been studied in bacterial cells using electron microscopy and biochemical methods and found to involve rapid cytoplasmic partitioning, nucleotide coagulation, and loss of enzymatic activity. The cells did not completely decompose, but pores appeared in the cell wall, causing leakage of cellular components (Schreier et al., 1997). The wide range of uses of iodophor makes it possible to create various iodine-polymer compositions: solutions, ointments, foaming creams, films, mucoadhesive tablets, etc. Iodophors are stable during long-term storage, and their side effects are extremely rare (Cooper et al., 2007).

Iodine-polymer complexes are widely used in pharmacy, veterinary medicine, medicine, production of disinfectants, and environmental protection. As mentioned above, iodine is a universal antiseptic, but when it comes into contact with the skin, an irritating effect occurs, limiting its use. Iodine-containing polymers are devoid of this disadvantage and are used as disinfectants, antimicrobial and antibacterial agents.

Antibacterial activity of PVP-Iodine observed in the pH range of 2.5-7.0. In *vivo* studies have shown that PVP iodine kills 96.7 % of bacteria within 60 seconds of contact with the mucous membrane of the eye (Ferguson et al., 2003). PVP iodine has many of the properties required for wound treatment and has a wide spectrum of antimicrobial activity (Shiraishi et al., 1997), affecting viruses (Kawana et al. 1997), fungi (König et al., 1997) and parasites. PVP iodine does not cause resistance, is more effective against biofilms, is well tolerated, acts on inflamed areas of the skin and has excellent ability to form films (Kumar et al., 2009). Thus, iodophor is an ideal antiseptic for the treatment of skin and mucous membranes during preparation for surgery.

Severe acute respiratory syndrome caused by coronavirus (SARS-CoV) was first detected in November 2002 in Guangdong Province, China. The virus caused 774 human deaths between November 2002 and July 2003 (Kariwa et al., 2006). Antiviral activity against coronavirus was studied for povidone-iodine. Treatment of SARS-CoV with povidone-iodine preparations for 2 minutes reduced the infectious titer from 1.17×10^{6} $TCID_{50}$/mL (50 % infectious dose in tissue culture) to a level below the detectable limit. The efficacy of povidone-iodine was equivalent to that of 70% ethanol. As a preventive measure, the use of sprays and rinses with povidone-iodine is important. The new coronavirus SARS-CoV-2 appeared in the Chinese province of Wuhan in the last decade of 2019. On March 11, 2020, the World Health Organization declared SARS-CoV-2 a pandemic. Patients and healthcare professionals are encouraged to use sprays containing 0.5 % povidone-iodide, 0.28–0.30 ml in each nostril (Khutoryanskiy et al., 2010). The total dose of iodine in this case is approximately 0.33 mg and does not cause any side effects. Mouthwash with 9 ml of 0.5 % povidone-iodine solution for 30 s was suggested in (Poutanen et al., 2005). The total dose of iodine in this case is approximately 0.05 mg. It has been shown that a single injection of povidone-iodine leads to a decrease in the microflora of the oral cavity within 3 hours.

There are more than 400 brands of pharmaceuticals (generics) based on iodine-polymer complexes in the world (www.drugbank.ca/drugs/DB06812). The most common active ingredients are iodine complexes with PVP and PVA.

The non-adhesive INADINE dressing consists of a low-adhesion fabric impregnated with PEG and containing 10 % povidone iodine and 1 % free iodine. INADINE has been shown to be effective as a non-adherent antiseptic dressing for the primary treatment of wounded skin areas (Vermeulen et al., 2010). It has been established that iodine-containing dressings are superior to dressings with sulfadiazine and inferior to dressings with rifamycin. In addition, 5 % iodine-PVP ointment has been found to be superior to silver sulfadiazine in wound healing. The drug has been shown to be effective and well tolerated by pediatric patients (Lafferty et al., 2011).

Microbial infection of the burn wound can have a significant effect, as microorganisms can contribute to the progression of partial-thickness burns to full-thickness burns with severe consequences. PVP-iodine ointments have been used to treat patients with burns of various sizes in combination with antibiotics and systemic administration of vitamins E and C to alleviate oxidative stress in burn wounds (Al-Kaisy et al., 2005). Ointments containing PVP-iodine have shown an efficacy of 15.3 % and a wound healing time of 4 days. which made it possible to reduce the cost of staying in the hospital. Moreover, no side effects were observed. Of particular importance in patients with concomitant skin injuries (e.g., open bleeding) are the effects of PVP

iodine on neutrophils and oxygen radicals (Landsman et al., 2016) have developed polymeric hemostatic materials with shape memory based on the hydrogel PEG-acrylate-PVP-iodine to stop wound bleeding. Hydrogels increased fluid absorption by 19 times compared to hydrogels without povidone-iodine and showed high antibacterial activity. Hemostatic macroporous polymer foams were synthesized by tempering the highly dispersed (inner) phase of an emulsion based on PEG and sodium acrylate (Lundin et al., 2019). Polymer foams were impregnated with an iodine solution to impart antimicrobial activity. Prolonged iodine release over 48 h was achieved at higher iodine concentrations in solutions, whereas rapid release was observed at lower concentrations. The complexes showed activity against *the bacteria Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus*.

A complex of iodine with sodium acrylate and N-vinylpyrrolidone copolymers in combination with carboxymethylchitosan has been used to prevent postoperative infection after treatment of vaginal diseases (Chen et al., 2018). The results of clinical studies have shown that the composition under consideration is more effective than the standard treatment method.

Another promising area is the creation of new drugs for targeted delivery of iodine to hard-to-reach areas of the body and increasing the period of iodine action. For example, povidone-iodine has been found to be suitable for the treatment of conjunctival infections (Koerner et al., 2018). Another study demonstrated the efficacy of povidone-iodine against pathogenic vaginal bacteria (Moghadam et al., 2018).

Thus, it can be said that polymer-iodine complexes are widely used as effective antiseptics and antimicrobial agents in medicine and pharmacy. Structural modeling of the polymer carrier opens up new opportunities for the use of iodophores as antiseptic and antimicrobial agents in the treatment of various infectious diseases

The creation of new active pharmaceutical ingredients that have a wide range of action is an urgent problem. Knowledge of the physicochemical characteristics and structure of the drug is necessary in order to correctly interpret the mechanism of action and its behavior after administration into the body. The structure and properties of the drug, in the end, determine both the dosage form and the method of administration. In this regard, the purpose of our research was to study the structure and properties of APIs using a set of physicochemical methods.

Materials and basic methods

The object of the study is active pharmaceutical substances (hereinafter referred to as API) provided by the Scientific Center for Anti-Infective Drugs. The drug is a complex compound by its chemism, which is molecular and ionic complexes of iodine with associates of synthetic water-soluble polymers, as well as natural mono-, oligo- and polysaccharides and natural proteins. The total molecular weight of the drug is 55–60 kDa. 1000, 1:100 and 1:10. For potentiometric studies, solutions of potassium iodide salts 12.0 g/l, lithium chloride 4.0 g/l, calcium chloride 2.0 g/l, magnesium chloride 4.0 g/l were taken. Sigma Aldrich, Germany, 99.8 %).

Determination of the viscosity of API solutions

Viscometric studies of API solutions were carried out using a glass capillary temperature-controlled viscometer. The viscosity measurement temperature of solutions of various concentrations was 20, 25, 30, 35 and 40 °C. The dynamic viscosity of the solutions was calculated according to the following formula:

$$\eta = K \times \tau \quad (1)$$

where η - dynamic viscosity of solutions, CPZ;
K - viscometer constant, determined by the flow of distilled water;
τ - time for liquids to flow out of the capillary, in min

Determination of Electrical Conductivity

A Multi 340i conductivity meter was used to measure the electrical conductivity of API solutions. Previously, the readings of the device were checked on a standard solution of 0.01n KCl at appropriate temperatures. The drug dilutions of 1:2000-1:10 were used.

Potentiometric Titration of API Solutions

In order to determine the potential of API solutions when diluted with water, saline and electrolytes, a device was assembled, which consisted of a pH meter (universal ionomer EV-74) connected to an analog-to-digital converter (ADC) ADAM-4018M connected to a PC. The readings of the device were recorded in the computer using the ADC. A working electrode (platinum) and an auxiliary electrode (silver chloride) were lowered into the vessel with the liquid under study. The liquid used for titration of API solutions was also supplied here at a constant rate. Potential measurements were taken every 30 seconds. Further, the data were processed using the "Origin" program according to the formula for determining the dependence of the equilibrium concentration of the API solution on the time of measurement:

$$C = \frac{C_0}{1 + \frac{v_k}{V_0} \cdot \tau} \quad (3)$$

where C_0 – initial concentration of the API solution, equal 1:10, v_k – titration fluid delivery rate, л/с, V_0 – initial volume of API solution, equal 0,03 L.

Results and discussion

Viscometric studies of the medical drug API

Physicochemical studies of the drug, previously conducted studies have shown that API solutions are suspensions that have thixotropic properties. This property is characteristic of structured liquids, which is due to the presence of particles in the liquid medium. To study the features of the flow of such systems, as well as unstructured suspensions and sols, the method of capillary viscometry, which is common for liquids, is used, based on the measurement of the volumetric velocity of flow through the capillary.

The dynamic viscosity (η, CPZ) of the API solutions was measured with a temperature-controlled viscometer at dilutions with saline of 1:1000, 1:100 and 1:10. All solutions were pre-filtered. For comparison, the viscosity of the saline solution was also determined. Measurements were carried out at temperatures of 20, 25, 30, 35 and 40 °C. Figure 1 shows the viscosity relationship graph for water, saline and API at three dilutions. As measurements have shown, the viscosity of API solutions increases with an increase in concentration compared to saline, in general: the maximum values of η have an API solution with a dilution of 1:10.

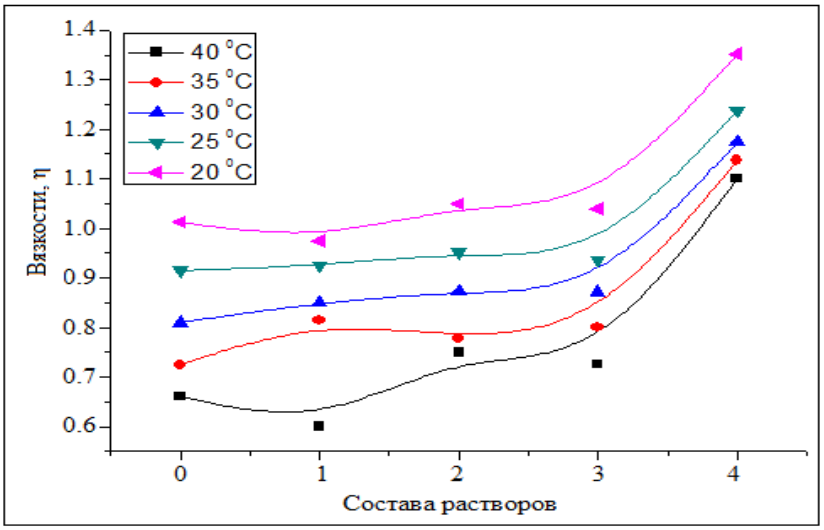


Fig. 1. Temperature dependence of viscosity on the composition of solutions: 1-H2O, 2-NaCl, 3-API 1:1000, 4-API 1:100, 5-API 1:10

Thr Einstein's law is usually used to describe the viscosity behavior of η dispersed system (sol, suspension):

$$(\quad - \quad _0)/ \quad _0 = k \qquad (4)$$

where η and η_0 – the viscosity of the colloidal solution and the pure dispersion medium; $\varphi=V_d/V$ – volume fraction of dispersed phase (V_d) in the total volume of the system (V); k - constant defined by the shape of the particles.

According to this law, the viscosity of such a system increases with the increase in the content of the dispersed phase. The physical meaning of this law is that the relative increment of viscosity is directly proportional to the relative content of the dispersed phase. The larger the φ value, the more vigorous is the inhibitory effect of particles (which do not have internal fluidity) on the flow. With linear dependence η from φ liquids are referred to as ordinary, or Newtonian liquids. Structured colloidal systems are distinguished by the fact that they do not obey the laws of Newton and Einstein. For them, the viscosity value usually increases with an increase in the content of the dispersed phase much more. They are also called non-Newtonian fluids [2].

Figure 1 shows the regularity characteristic of structured liquids quite well: with an increase in the content of the drug, the viscosity of solutions increases sharply. Moreover, with an increase in temperature, this effect is even more pronounced, which is probably due to an increase in the number of particles in the volume of the API solution compared to lower temperatures. Below are graphs of the dependence of the viscosity of solutions on temperature (Fig. 2 and 2-A).

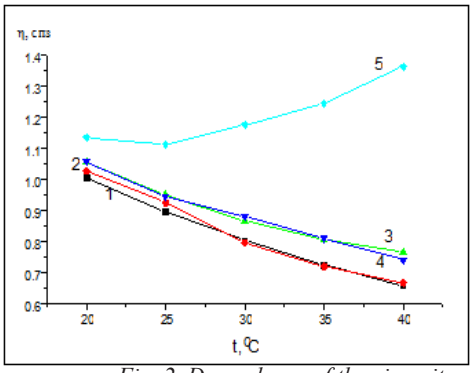


Fig. 2. Dependence of the viscosity of solutions: API on dilution without washing the capillary. 1- H_2O, 2- NaCl, 3-API 1:1000, 4-API:100, 5-API 1:10

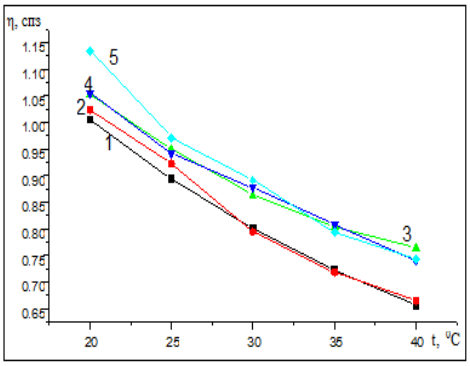
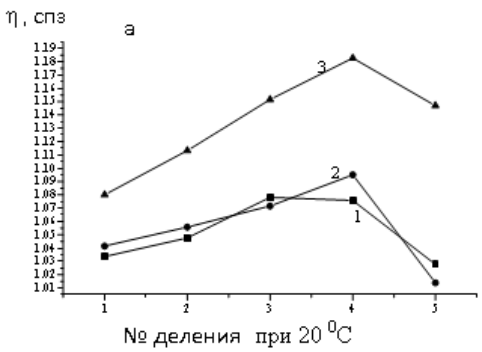
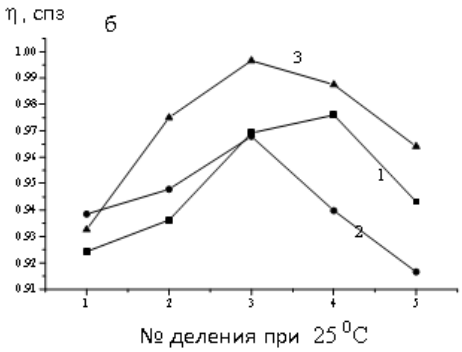


Fig. 2A. Dependence of the viscosity of API solutions on dilution: 1- H_2O, 2- NaCl, 3-API 1:1000, 4-API 1:100, 5-API 1:10

With an increase in temperature, the viscosity of all solutions decreases, and at temperatures from 20 to 250 °C, sharper decreases in values are observed in comparison with their change in the range of 25–400 °C. It should be noted here that this viscosity behavior is more clearly manifested for the concentrated API solution itself. With a decrease in the content of the drug, this phenomenon is leveled out.

During the measurement, an interesting feature of the viscosity change for the concentrated solution itself was noted: if the viscometer capillary was not washed before each measurement, then the effect of increasing viscosity in subsequent measurements was manifested. This phenomenon was not observed with constant flushing of the capillary: viscosity naturally decreased with an increase in temperature. Most likely, at a given concentration of API, the thixotropic properties of the solution are manifested, i.e. the structuring ability for it remains high even after filtration. The time of discharge was measured sequentially one after another without flushing the capillary in order to verify the possibility of structuring during viscous outflow through the capillary. The results are presented in Fig. 3.





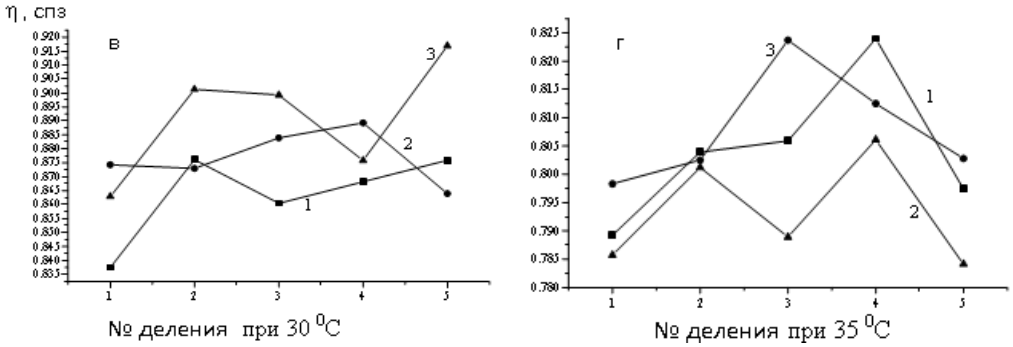


Fig. 3. Curves of changes in the viscosity of API solutions depending on the number of consecutive measurements:1-API 1:1000, 2-API 1:100, 3-API 1:10

Thus, the temperature dependence of viscosity can be conditionally divided into two rectilinear sections that have different angles of inclination. In general, this curve indicates that the system is undergoing a process of disaggregation. It is likely that the large micelles present in the solution (especially in the 10-fold diluted API) break down into smaller particles throughout the measurement process, with disaggregation being most intense at temperature range of 20–25 °C.

As can be seen from the above data, in general, there is a noticeable trend towards an increase in the elapse time from the number of the sequential measurement. This behavior may be due to the fact that the structuring of the gel in solution occurs from the walls where the adsorption of particles begins, which leads to the effect of reducing the diameter of the capillary.

We tried to calculate the activation energy of a viscous flow (E_A), for what a dependency graph was built lgη from reverse temperature (Fig. 4), and then, using the tangent of the angles of inclination of the lines drawn over the two sections, their values for all solutions of API are determined (Table 1).

Table 1. Calculation of viscous flow activation energy

Composition of solutions	Ea, kJ/mol (Range of temperature 20–25 °C)	Ea, kJ/mol (Range of temperature 25–40 °C)
Water	6,88	
Saline solution	7,20	
API in 1000 s	4,75	6,31
API in 100 s	5,30	6,98
API in 10 s	6,02	9,57

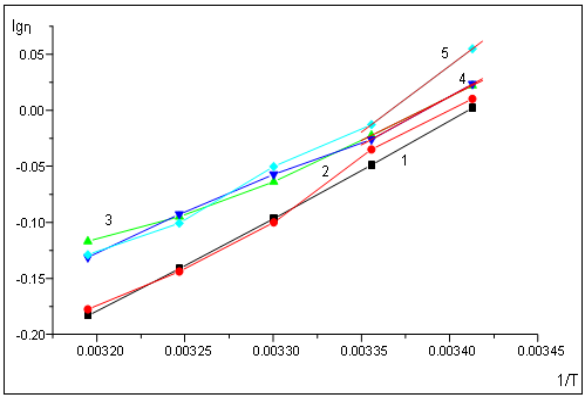


Fig. 4. Dependence of viscosity logarithm from its temperature: 1- H2O, 2- NaCl, 3-API 1:1000, 4-API 1:100, 5-API 1:10

However, the activation energy calculated from the initial ranges of the (temperature 20–25 °C) for solutions the API was less than for pure saline. If for saline E_A=7,20 kJ/mol, then for an API solution diluted 100 times, it has a value of about 5 kJ/mol. Such a decrease $E_{A,}$ is probably due to the fact that during the breakdown of micelles into smaller, part of the molecules NaCl is spent on the formation of new solvate layers. This leads to a decrease in the number of free molecules in the system NaCl, as a result of which E_A API solution drops. Further, with an increase in the concentration of APC, the activation energy increases slightly, reaching the value of 6,02 kJ/mol. The increase in the values of the activation energy is due to an increase in the number of particles in the volume of the liquid.

Thus, the data of viscometric studies prove unequivocally that API solutions are structured liquids. This property of solutions is due to the presence of particles in the liquid volume, the size of which can be different. Presumably, the particles are rather large micelles (the shape of which can also be very diverse), capable of decaying into smaller particles under the influence of both mechanical action and temperature.

Measurement of electrical conductivity of API solutions

We measured electrical conductivity on API solutions at three dilutions: 1:1000, 1:100 and 1:10 at the same temperatures as in viscometric studies at the beginning. At the same time, the measurement technique was worked out, since the conductivity meter is designed to measure electrical conductivity at temperatures 20–25 °C.

Fig. 5 shows the data on the dependence of specific electrical conductivity (χ) from temperature. The graph shows reference data on the solution for comparison KCl. As can be seen, the electrical conductivity of saline and API with dilution 1:1000 match, but for API (1:100) values χ are lower. This change is most likely due to micelle formation, which leads to a decrease in the number of conductive particles due to their aggregation. The next API solution (1:10) has relatively high conductivity values. This indicates an increase in the number of electrically conductive particles with an increase in the concentration of the drug.

The general pattern for all solutions is that with an increase in temperature, electrical conductivity also increases. Such a change in the electrical conductivity of solutions is quite natural, because with an increase in temperature, the viscosity decreases

and the freedom of movement of electrically conductive particles increases. Similar to viscometric studies, the activation energies of electrical conductivity were also determined here (Fig.6, Table 2).

As can be seen from the table, there is a slight decrease in the values of the activation energy of API solutions compared to saline, which is natural, since with an increase in the concentration, the number of particles capable of conductivity increases.

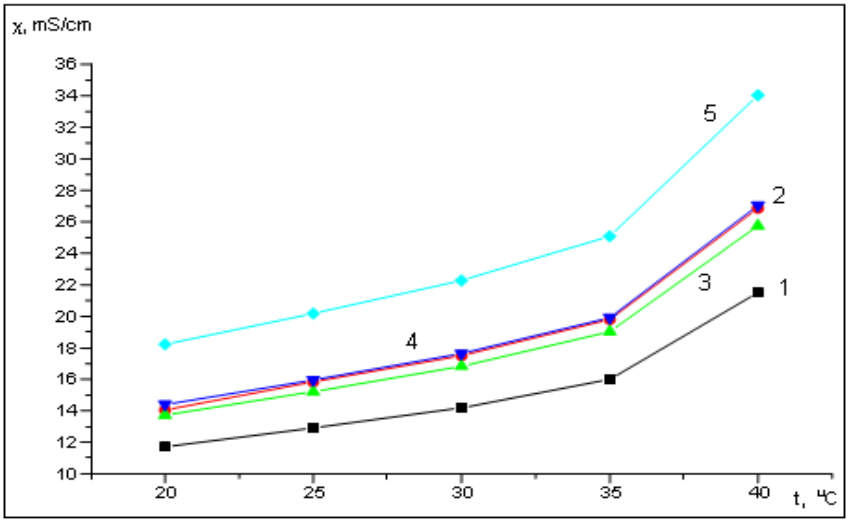


Fig. 5. Change in the electrical conductivity of solutions with temperature: 1. KCl, C=0,1 n.; 2. Saline; 3. API in 1000 s.; 4. API in 100 s.; 5. API in 10 s.

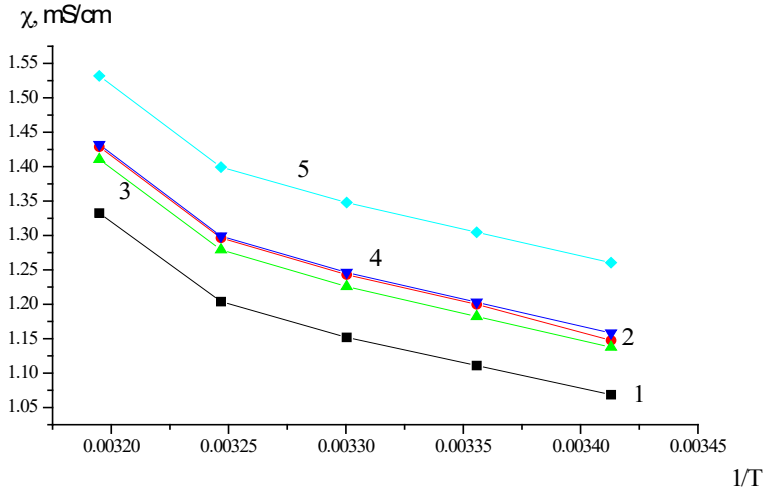


Fig. 6. Dependence of the logarithm of electrical conductivity on the inverse temperature. 1. KCl C=0,1 n, 2. Saline, 3. API in 1000 s., 4. API in 100 s., 5. API in 10 s.

Table 2. Calculation of activation energy of electrical conductivity

Composition of solutions	Ea, kJ/mol (Range of temperature 20–35 °C)
KCl 0,1 n.	6,53
Saline	7,15
API in 1000 s	6,84
API in 100 s	6,81
API in 10 s	6,71

Taking into account the available data, we calculated the value of electrical conductivity corrected for viscosity. The results are shown in Figure 7. Since the corrected electrical conductivity is a characteristic of the number of conductive particles and taking into account the fact that the total concentration of the electrolyte component at 10-fold dilution does not provide a significant addition of conductive particles, it is necessary to conclude that the increase in the mobility of new ions makes a significant contribution to the resulting effect. As can be seen from the figure with an increase in temperature, the electrical conductivity corrected for viscosity increases. With an increase in the concentration of the drug, its values also increase. It should be noted here that on the graph, the curves pass through small lows, which appear brighter with an increase in the concentration of API. The increase in corrected electrical conductivity with temperature clearly indicates the disaggregation of particles.

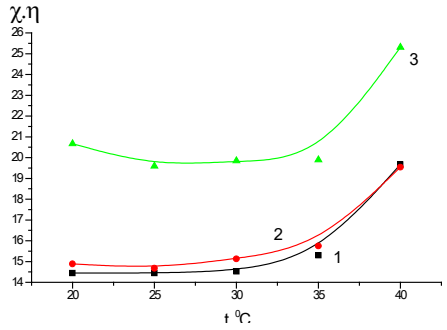


Fig. 7. Dependence of corrected electrical conductivity on temperature. 1-API in 1000 s, 2-API in 100 s, 3-API in 10 s (dilution with saline).

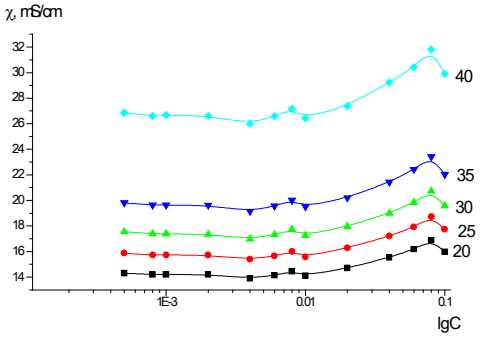


Fig. 8. Specific electrical conductivity of API solutions with different dilutions

Further, the electrical conductivity was measured at the same temperatures when diluted with a saline solution of API from 1:2500 to 1:10 (Fig. 8). The curves of changes in electrical conductivity with an increase in the content of the drug tend to increase. This indicates an increase in the number of electrically conductive particles with a concentration. As we expected, there are several minima at APC concentrations on the conductivity curves 8×10^{-3}, 4×10^{-2}, 1×10^{-2} and 0,1. The appearance of these minima is associated with the processes of micelle formation, which leads to a decrease in the number of electrically conductive particles.

Potentiometric study of the stability of solutions of the preparation API

The meaning of the method is that with the help of a redox indicator electrode,

the role of which is played by platinum, the redox potential of the system formed by solutions of the drug in salts of various concentrations is measured.

To find out the change in redox properties, titration was carried out with solutions of salts included in the preparation in order to identify the individual effect of each of them. Salt solutions were used: NaCl, LiCl, $MgCl_2$, $CaCl_2$ и KI. In addition, titration with ordinary distilled water was carried out for comparison.

Figures 9–15 show the curves of the dependence of the redox potential of the system on the concentration of the drug in conventional units, which practically denote the value inverse to the dilution of the original preparation API. In semilogarithmic coordinates, the main part of the curve is a straight-linear section with an angle of inclination close to the angle of inclination for an electrochemical reaction with a single-electron transition. Moreover, the angle of inclination is also close to the value for a single-electron junction. This behavior can be explained by the fact that the reaction by which this process can be described involves a certain equilibrium associated with the molecular and ionic forms of iodine, depending in this case on dilutions or concentration ratios.

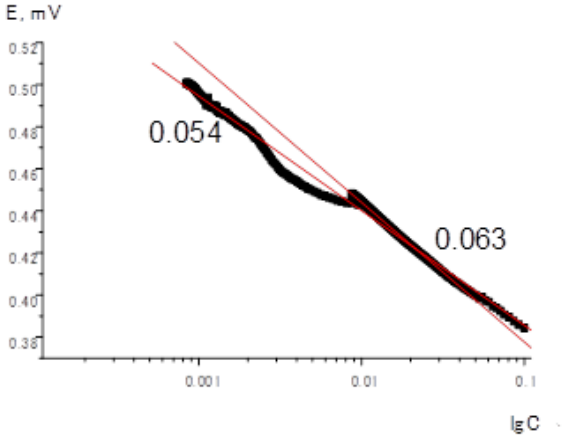


Figure 9. Potentiometric titration of API solutions with water

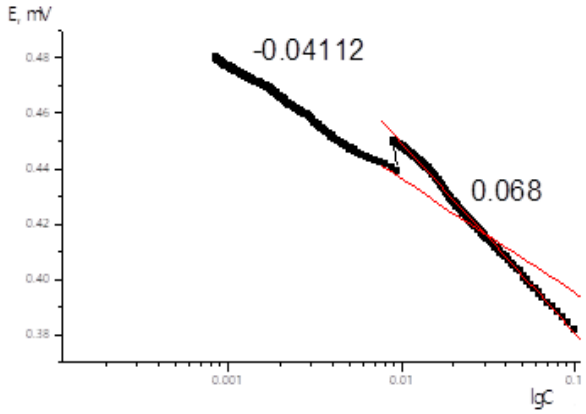


Figure 10. Potentiometric titration of solutions of the drug product API with NaCl solution

Similar curves that were obtained during titration of NaCl (Fig. 10) and LiCl (Fig. 11) have some differences, perhaps not so significant, which consist in a decrease in the angle of inclination of the curve during dilution.

An even more pronounced difference is the titration curves of API solutions with divalent metal solutions, i.e. $MgCl_2$ (Fig.12) and $CaCl_2$ (Fig.13). At the same time, there is a clear curve break, at approximately the same concentration for both solutions, at dilutions of about 1/200, which coincides with the presence of cash registers in that area, and at the same time there is a change in the angle of inclination, which for $MgCl_2$, can be represented as a transition from one-electron equilibrium to two-electron equilibrium, and for $CaCl_2$ from single-electron, to an even greater value.

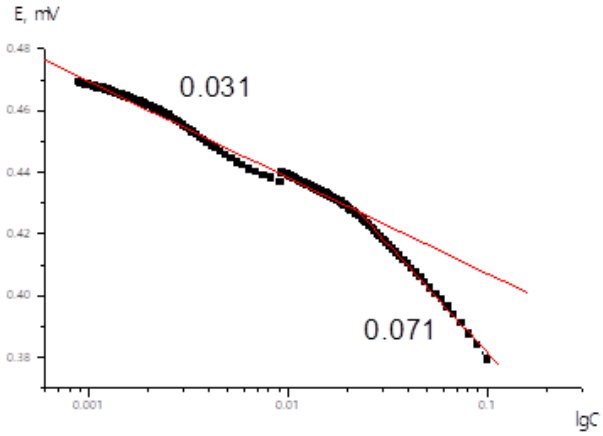


Figure 11. Potentiometric Titration of API solutions with LiCl solution

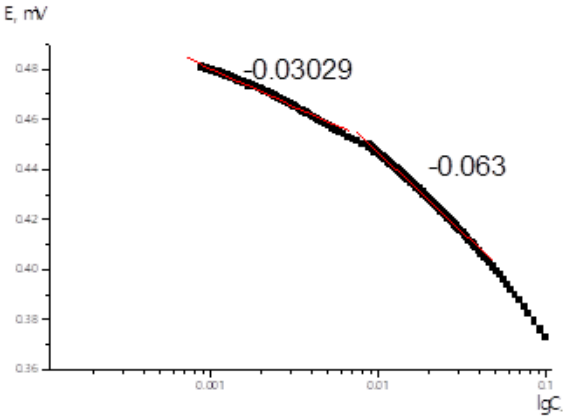


Figure 12. Potentiometric titration of solutions of the drug product API with $MgCl_2$ solution

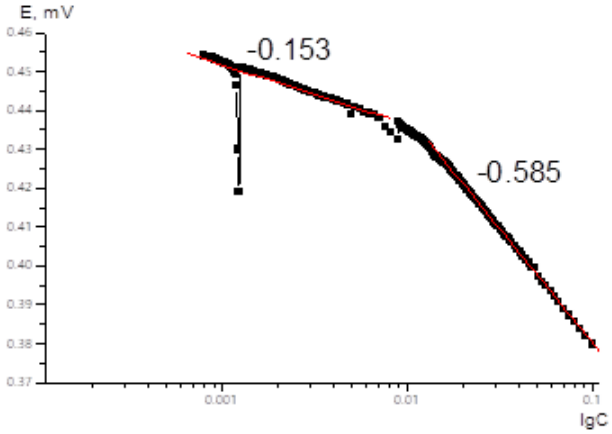


Figure 13. Potentiometric titration of solutions of the drug product API with $CaCl_2$ solution

If we analyze the type of dependence from the point of view of equilibrium on the electrode, then it can be described on the basis of the assumption of the constant activity of the oxidized form of iodine, i.e. molecular iodine, and the activity of the reduced form, i.e. J^-, which changes during dilution during titration and as it should be in this case, the slope of the curve should be according to the Nernst equation - 0.59 mV by an order of magnitude, and the angle of inclination should be negative, which we see in this case. For example, for the cations Li^+, Mg^{2+} and especially Ca^{2+}, the inclination angle begins to drop sharply with increasing dilution. This behavior may indicate that with large ratios of the concentration of I^- to the concentration of ions of the titratable solution, i.e. Ca^{2+}, Mg^{2+} and Li^+ ions, a significant part of J^- can fall into the sphere of complexation of these very titrative agents and there is an effective decrease in concentration.

Another explanation for the change in the angle of inclination of the dependence may be that in the area of about 200 dilutions, where this transition is most often observed, we just observe the rearrangement of micelles. On the curves of the dependence of surface tension on composition, we have fracture points associated with their realignment. In addition, if we consider in more detail the course of the curves during titration with water, NaCl, LiCl, we can see that kinks also exist at dilutions of the order of 700, 800, which also corresponds to the critical concentration of micelation found in other experiments. The same can be seen in the titration curves with $CaCl_2$ solution. A similar kink in the dependence is present on the titration curve $MgCl_2$. Changes in the angle of inclination with a change in the concentration corresponding to the rearrangement of micelles may well be due to the fact that a change in the structure of the aggregate cause's different types of equilibrium of this aggregate with the solution, in any case, differences in these equilibriums, which is reflected in the angles of inclination. Judging by the fact that this is characteristic for divalent cations and partly for Li, it can be assumed that particles with more pronounced acidic properties largely determine the very process of micelle formation.

In general, a change in the angle of inclination on potentiometric curves indicates that the process passes from the region of constant activity J^2 in the solid phase to the region where a change in the concentration of some component of the solution (in particular, Mg^{2+} and Li^+) leads to a change in the activity of molecular iodine to the solid

phase, i.e. micelle. The question of the equilibrium of the system should be touched upon separately, since the available data on dilution with water and physiological, as well as the initial sites for dilution with solutions of other salts, indicate that the system must be equilibrium. Therefore, with a high degree of probability, it can be assumed that the changes that occur with the micelle during titration with salts containing rather acidic cations are due to the fact that these cations are additionally incorporated into the composition of the micelles and lead to a decrease in the activity of molecular iodine in it, which is manifested in a change in the angle of inclination.

The most unexpected dependence was obtained during titration with KJ solution (Fig. 14–15). The course of the relationship corresponds to a formal increase in the activity of the oxidant in the solution, which can be easily explained by the fact that an increase in the concentration of KJ (compared to other components) leads to a shift in equilibrium towards the extraction of molecular iodine from micelles in the form of tri-iodide. If we recalculate the titration curve for the dilution of the iodide ion in the solution of the preparation, we get a curve with a slope very close to the theoretical slope for J^- (Fig. 15). Later, at high concentrations, the dependence breaks down, and the main factor in this balance begins to be the complexation of iodine from the micellar state.

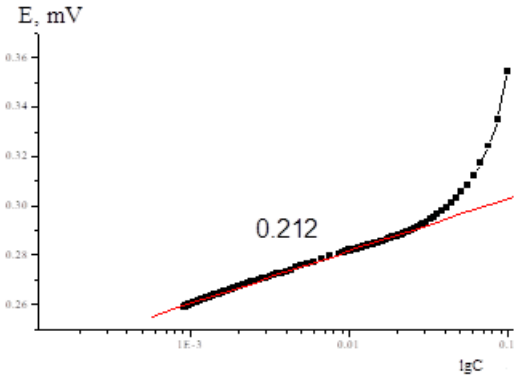


Figure 14. Potentiometric Titration of API-1 Solutions with KJ Solution

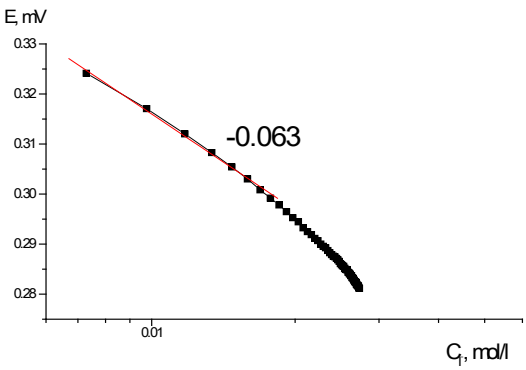


Figure 15. Potentiometric titration of solutions of the drug product API with KJ solution, recalculated for dilution of the iodide ion

Summarizing all of the above, it can be concluded that potentiometric measurements allow us to assume that iodine in oxidized form is in the form of particles with its constant activity in phase, i.e. micelle. This is possible if this iodine is packed inside the micelle and at the same time is in connection with J^-, which are located in the outer shell of the micelle, giving it a negative charge, which entails the disintegration of the micelles as such and its rearrangement into different forms. In order for this aggregative state to be stable, it is probably not enough to have only an organic component or only molecular iodine in the nucleus. Most likely, it is some kind of combination consisting of organic molecules, in which a complex of tri-iodide ion with a metal cation is enclosed, for example Mg^{2+}, Ca^{2+}, Li^+.

Conclusion

1. As a result of viscometric studies, it was established that API solutions are non-Newtonian liquids characterized by the presence of structures. With an increase in temperature, the viscosity of solutions decreases. On these curves, there is a slight break, which indicates the course of the processes of disintegration or disaggregation of existing structures or associations. This effect is also confirmed by the data of calculations of the activation energies of the viscous flow (E_a).

2. Measurements of the electrical conductivity of API solutions show that with increasing drug content, the χ value increases. This is due to an increase in the number of electrically conductive particles in the system, which occurs both due to the concentration of solutions and due to the disaggregation of micelles. On the curves of the dependence of electrical conductivity, four minima were found at dilutions of 1:1200, 1:250, 1:100 and 1:10. The appearance of minima is associated with the processes of micelle formation, which lead to a decrease in the number of electrically conductive particles.

3. Potentiometric studies of the stability of API solutions suggest that iodine in an oxidized form with constant activity is located inside the micelles. At the same time, it is in a certain ratio with iodine anions located in the outer membrane of the micelle, thereby giving it a negative charge, which entails the disintegration of the micelles as such and its rearrangement into different forms. The stability of these aggregates is probably ensured by a combination of organic molecules in which a complex of tri-iodide ion and metal cations is enclosed.

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ХИМИЯ

СОДЕРЖАНИЕ

ФИЗИКА

ХИМИЯ

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