Journal of Organic and Pharmaceutical Chemistry

Original Research

OPEN ACCESS
Freely available online on
http://ophcj.nuph.edu.ua

UDC 543.2

I. R. Bondarets, V. A. Georgiyants
National University of Pharmacy of the Ministry of Health of Ukraine,
53 Hryhorii Skovoroda str., 61002 Kharkiv, Ukraine

The Experimental Study of the Quality and Safety of Injectable Implant Medical Devices Based on Hyaluronic Acid in Accordance with the Requirements of the EU Regulation

Abstract
The aim of the article is to present the results of the experimental study of leachables used as primary packaging for medical devices, namely injectable implants based on hyaluronic acid. For the study, a line of injectable implants with identical qualitative composition and differing quantitative hyaluronic acid content was used. When developing the research conditions, the main characteristics of the implant gel were taken into account, and the conditions for using the appropriate medical device were modeled to obtain the most informative results and confirm the safety of the primary packaging selected. The analysis of extracts was carried out using the following methods: GC/MS, HPLC/UV/MS, ICP/MS, and IC. No substances listed as Chemicals of Potential Concern were detected in the extracts obtained, thereby confirming the safety of using the medical device for the patient under the conditions specified by the manufacturer.
Keywords: quality control; safety; hyaluronic acid; chromatography

І. Р. Бондарець, В. А. Георгіянц
Національний фармацевтичний університет Міністерства охорони здоров'я України,
вул. Григорія Сковороди, 53, м. Харків, 61002, Україна

Експериментальне дослідження якості та безпечності ін'єкційних імплантатів на основі гіалуронової кислоти відповідно до вимог Регламенту ЄС

Анотація
Мета статті – викласти результати експериментального дослідження вилуговуваних речовин із первинного паковання медичних виробів, а саме ін'єкційних імплантатів на основі гіалуронової кислоти (ГК). Об'єктом дослідження була лінійка ін'єкційних імплантатів, які мають ідентичний якісний, але відмінний кількісний склад за вмістом ГК. Щоб отримати високу інформативність результатів і підтвердити безпечність використання обраного первинного паковання, під час розроблення умов експерименту враховували основні характеристики гелю імплантатів, а також моделювали умови застосування відповідного медичного виробу. В отриманих зразках не виявили речовин, що належать до потенційно небезпечних. Отже, було підтверджено безпеку використання медичного виробу для пацієнта за умови дотримання інструкцій, зазначених виробником.
Ключові слова: контроль якості; безпечність; гіалуронова кислота; хроматографія

Citation: Bondarets, I. R.; Georgiyants, V. A. The Experimental Study of the Quality and Safety of Injectable Implant Medical Devices Based on Hyaluronic Acid in Accordance with the Requirements of the EU Regulation. *Journal of Organic and Pharmaceutical Chemistry* **2025**, *23* (3), 28–35.
https://doi.org/10.24959/ophcj.25.339976
Received: *3 August 2025*; **Revised:** *29 September 2025*; **Accepted:** *4 October 2025*

Funding: The author received no specific funding for this work.
Conflict of interests: The authors have no conflict of interests to declare.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Introduction

Injection implants have become widely used in current medical practice. Regardless of the purpose – medical or cosmetic – the manufacturer is responsible for the product's quality and safety.

The quality of any medical devices is ensured at the stage of their production. Previously, we validated the technological process for manufacturing injectable implants based on hyaluronic acid [1, 2]. It included a theoretical risk assessment at the first stage and direct validation at identified critical points at the second stage.

The most significant safety risks in the use of medicines and medical devices are impurities. These impurities can have different origins; therefore, during implementation and development, it is mandatory to take into account all factors that may contribute to the formation of associated and extraneous impurities and to implement appropriate measures to regulate them. The highest risk is also noted for parenterally administered medical devices [3]. One of the focuses of the recently entered into force European Union Regulation (EU) 2017/745 (MDR) is compliance with the safety standards for medical devices to minimize harm to patients when used for their intended purpose [4]. The biocompatibility assessment is a key element in confirming the safety of products for the human body [5]. In accordance with the requirements of the MDR [4], manufacturers of medical products must conduct studies to confirm the medical device's ability to interact with the patient without causing harm.

One source of hazardous impurities in the use of medical devices is the containers used, such as syringes. Therefore, one element of biocompatibility research is the assessment of the physical and chemical properties of materials, namely the determination of extractable and leachable substances from the primary packaging of a medical device during its shelf life [6–9].

Research on leachable substances is always a scientific challenge, since the extraction of substances from packaging by common solvents of various natures can be predicted. Still, the extraction of substances under the influence of the product itself cannot. For some medical devices, this information is extremely limited [10].

This article presents the results of the study of leachable substances, i.e., those that can be released from the primary packaging of a medical device during its use under the influence of temperature, environment, and other operating conditions, and enter directly into the composition of the medical device itself. Such substances can enter the patient's body and potentially cause undesirable reactions or toxic effects.

For injectable implants, this is critically important, given that such devices are introduced into the human body and remain there until they are completely biodegraded [11]. The safety threshold is 0.15 µg per day for genotoxic or carcinogenic compounds and 1.5 µg per day for others [4]. Depending on the nature of such substances, an adequate method for their detection should be chosen.

The use of hyaluronic acid in various medical devices has continued to expand in recent years, as evidenced by numerous publications on its efficacy and safety [12–15]. At the same time, there are few experimental studies in the literature on the detection of substances extracted or leached from the primary packaging of medical devices. Studies of leachable substances from primary packaging should be conducted by medical device manufacturers at the design and development stage of the product, as well as when making critical changes that could affect the product's physicochemical parameters. Manufacturers are likely to be reluctant to disclose this information. This article presents a description of the methods and results of studies on leachable substances from the primary packaging of medical devices – injectable implants based on cross-linked hyaluronic acid.

Thus, the aim of this article was to demonstrate the research results on leaching chemicals that may pose a potential hazard to the patient in medical devices – injectable implants in pre-filled syringes. The studies were conducted on a finished medical device (a pre-filled syringe with gel).

Materials and methods

Equipment and reagents

To determine the conditions of the study, the following characteristics of the medical device were taken into account:

- *the pH value* – the limits of the line of injectable implants studied – 7.2–7.4 (physiological pH);
- *duration of contact of the implants with the human body* – long term (> 30 days);
- *the type of medical device* – risk class III, implantable product;
- *the shelf life* – 2 years;
- *storage conditions* – from +2 °C to +30 °C.

The algorithm for conducting the study of leachable substances was as follows [16]:

1. Selection of the research material – assessment of primary packaging materials and the medical product composition.

2. Determination of research conditions and methodology – development of an analysis method, research conditions, and determination of the required list of equipment.

3. Conducting the research:

3.1. Modulation of the conditions of use of the finished medical device – to simulate the worst case, a sample of the medical device that was in climatic chambers and underwent product stability studies was used. Thus, samples simulating the medical device at the end of its shelf life (2 years) and with a storage temperature at the upper limit (+30 °C), i.e., the longest contact with the primary packaging expected by the manufacturer, were used;

3.2. Analysis of the components released – the quantitative and qualitative analysis in the samples of substances that could have leached from the primary packaging into the gel of the medical device. The following methods were used for the analytical study:

- head-space gas chromatography for the determination of volatile substances (an Agilent RTX-624 capillary column – 30 m × 0.25 mm, the aliquot volume – 1.0 mL, the ejector temperature – 200 °C, the flow rate – 1 mL min^{-1}, helium as a carrier gas, the GC temperature program – from 40 °C to 240 °C at a rate of 8 °C min^{-1});
- gas chromatography coupled to a mass spectrometric detector (GC/MS) for the determination of semi volatile organic compounds (an Agilent HP-5MS capillary column – 30 m × 0.25 mm, the aliquot volume – 1.0 mL, the injector temperature – 280 °C, the flow rate – 1.0 mL min^{-1}, helium as a carrier gas, the GC temperature program – from 40 °C to 280 °C at a rate of 10 °C min^{-1}, then to 310 °C at a rate of 15 °C min^{-1});
- liquid chromatography coupled with UV and mass spectrometric detectors (HPLC/UV/MS) for the determination of non-volatile organic compounds (an Agilent Zorbax Eclipse XDB-C18 column – 2.1 mm × 50 mm, the aliquot volume – 5 µL, 5 mM ammonium acetate in water and 50:50 MeCN/MeOH (*v*/*v*) were used as the mobile phase, the mobile phase speed – 0.4 mL min^{-1}, the temperature – 380 °C, an UV detector – 210 nm; MS ESI+ and ESI–);
- inductively coupled plasma mass spectrometry (ICP/MS) for metal determination (Data acquisition parameters: the data acquisition mode – spectrum; peak pattern – 3 points; repetition – 3; repetition – 100; the stabilization time – 20 sec; the resolution – standard).

The results of the study were calculated as µg of the extracted product in 1 mL of the product.

4. Evaluation of the results obtained – assessment of the toxicological impact of the components found in the solutions and determination of the safety of the selected materials for the medical device.

To conduct a chemical characterization study, the threshold – the Analytical Evaluation Threshold (AET) – was calculated below.

Determination of AET for the GC/MS and HPLC/UV/MS methods:

$$\mathrm{AET}\left(\frac{\mu g}{mL}\right) = \frac{20\left(\frac{\mu g}{\mathrm{day}}\right) \times \frac{1}{2\ \mathrm{mL} \times 1 \times 1}}{2} = 5\ \mu g\ mL^{-1}$$

Each of the above methods was analyzed with the reference solution, test sample, and blank solution.

The limits of quantification for the metals studied, expressed in µg L^{-1}, are given in **Table 1**.

Sample preparation

Research on volatile organic compounds

To prepare the reference solution, an intermediate solution was prepared by diluting 0.2 mL of the toluene solution to 20 mL with water. Then, 0.5 mL of the intermediate solution was diluted to 50 mL with water. An aliquot of 5 mL of this solution was placed in a vial with a sealed test tube for analysis.

To prepare the test sample, an aliquot of the gel from the medical device, obtained after studying its stability under the conditions specified by the manufacturer in the primary packaging, with a volume of 1 mL, was mixed with 4 mL of water (dilution 1:5).

The resulting solution was placed in a 20 mL sealed test tube and analyzed without further processing.

The sample was prepared in duplicate.

Water was used as a blank solution.

Table 1. Limits of the metal quantification

Metal	Limits of quantification, µg L^{-1}
Li, V, Co, As, Mo, Ru, Rh, Cd, Os, Ir, Pt, Tl	0.10
Ni, Cu, Se, Sn, Sb, Ba, Pb	0.50
Ag, Hg	1.00
Cr, Pd, Au*	5.00

Note: *the sample solution after 50-fold dilution

ISSN 2308-8303 (Print) / 2518-1548 (Online)

The study of semi-volatile organic compounds

To prepare the reference solution, an intermediate solution was prepared by diluting 0.5 mL of the phenanthrene-d_{10} solution to 5 mL with dichloromethane (DCM). 0.1 mL of the intermediate solution was diluted to 10 mL with DCM. This solution was used as the AET of the analytical evaluation.

To prepare the test sample, two 5 mL aliquots of the gel samples from the medical device, obtained after stability testing under the conditions specified by the manufacturer in the original packaging, were mixed with 5 mL of DCM using a laboratory shaker (shaking time – 1 min). One mL of the organic phase was mixed with 4 mL of DCM (5-fold dilution). The resulting solutions were analyzed without further treatment.

An aliquot of DCM was used as a blank solution.

The study of non-volatile organic compounds

A mixture of the standard reference solution Irganox® 1098 and Reserpine (1 μg mL^{-1}) was used as a reference solution.

To prepare the test sample, 1 mL of the medical device gel, obtained after stability testing under the manufacturer's specified conditions in the original packaging, was diluted 5 times with water to a final volume of 5 mL and analyzed without further treatment.

An aliquot of H_2O was used as a blank solution.

The metal content study

As reference solutions, 0.5 mL of the certified standard solution (1000 mg L^{-1}) for each metal and 1.0 mL of concentrated HNO_3 were diluted to 50.0 mL with water.

To prepare the test sample, 1 mL of the medical device gel, obtained after stability testing under the manufacturer's specified conditions in the primary packaging, was mixed with 3 mL of HNO_3 and digested using the microwave procedure. The samples obtained were diluted to 50 mL with water (dilution 1:100).

To prepare the blank solution, 1 mL of H_2O was mixed with 5 mL of HNO_3 and digested using the microwave procedure. The resulting solution was diluted to 50 mL of H_2O (dilution 1:100).

■ Results and discussion

This article presents a study of substances leached from the primary packaging for a group of injectable implants (**Table 2**), using one product line as an example, which was determined to be the worst case (highest sodium hyaluronate content and highest daily dose).

The object of the study was an injectable implant based on cross-linked hyaluronic acid containing 20 mg mL^{-1} sodium hyaluronate, delivered in a prefilled syringe. To assess potentially hazardous substances, the composition and properties of the materials used in all components of the syringe should be considered. The syringe manufactured by Becton (Dickinson & Company) consists of a borosilicate glass cylinder, a bromobutyl rubber seal, and a polyisoprene rubber cylinder tip. The silicone covering the inner space of the cylinder, to facilitate smooth movement of the seal and piston, was also considered. Thus, all components of the primary packaging that come into contact with the medical device during its storage under the conditions specified by the manufacturer are subject to investigation. The manufacturer of hyaluronic acid is confidential information of the medical device manufacturer. However, the manufacturer has completed the internal qualification procedure and meets all the requirements.

It is known that hyaluronic acid can promote the release of substances, such as mangiferin, from polymers [16]. Such information creates a prerequisite for releasing other organic substances from packaging.

These studies aim to identify and control chemicals that may pose a hazard. These chemicals may have harmful effects on the patient's health and the environment. Their list is compiled by organizations, such as the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), the Organization for

Table 2. The group of medical devices under study: injectable implants based on hyaluronic acid

Product name	Sodium hyaluronate, mg mL^{-1}	Volume of primary packaging, mL	Sodium hyaluronate, mg
Injectable implant based on hyaluronic acid	15	1	15
	17.5	1	17.5
	20	1	20
	20	2	40

Economic Co-operation and Development (OECD), the European Chemicals Agency (ECHA), the United States Environmental Protection Agency (EPA), etc., and includes substances that meet at least one of the following criteria:

- carcinogenicity, mutagenicity or toxicity to the reproductive system;
- endocrine-disrupting properties that may have a negative impact on the hormonal system;
- persistence, bioaccumulation and toxicity;
- hazardous properties for ecosystems.

A theoretical assessment of the probability of leaching of harmful substances preceded the study. Based on the results of the forecast, we selected groups of substances that could be leached from the packaging according to the groups: semi-volatile, volatile substances, and metal impurities. The potential impact of substances on the patient was predicted using various mathematical models [17].

Research on volatile substances

In medical devices containing hyaluronic acid, as a rule, volatile organic compounds used in the production of raw materials, the finished product, or during its storage may be present. In particular, these may include alcohols, aldehydes, ketones, and essential oils used to flavor cosmetics. In this case, such substances were not used in the production of the injectable implant. However, volatile solvents, such as ethylene glycol, methylene chloride, and perchloroethylene [18, 19], may be used during the production of hyaluronic acid raw materials. Such substances may remain in the final raw material product and thus enter the finished medical product.

For volatile substances that are leached, the headspace gas chromatography-mass spectrometry method is traditionally used [20]. The leaching of volatile substances was evaluated compared to toluene at a concentration of 5 μg mL^{-1}. During chromatography of the test solution, no unidentified substance with a concentration greater than the standard was detected (**Figure 1**).

Research on semi-volatile organic compounds

The content of extraneous semi-volatile organic compounds was estimated by GC/MS. The substances were extracted from the hyaluronic acid solution with dichloromethane. The results were evaluated against the reference standard of phenanthrene added at a concentration of 5 μg/mL. Thus, any impurities with an area under the peak smaller than the reference are not subject to determination, while impurities with a higher content should be identified and determined.

As a result of the GC/MS study, no compounds with the content above AET were identified (**Figure 2**).

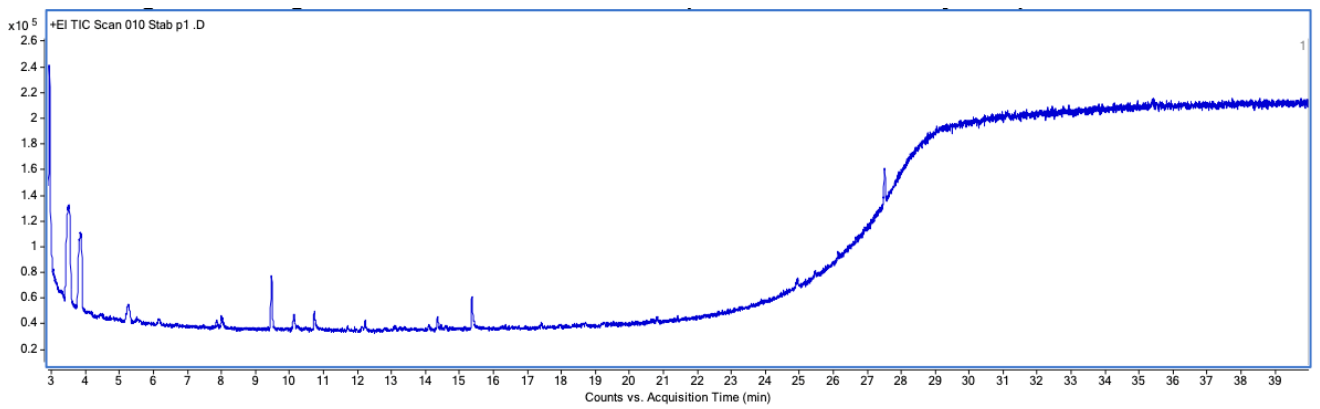

Figure 1. The chromatogram of volatile substances

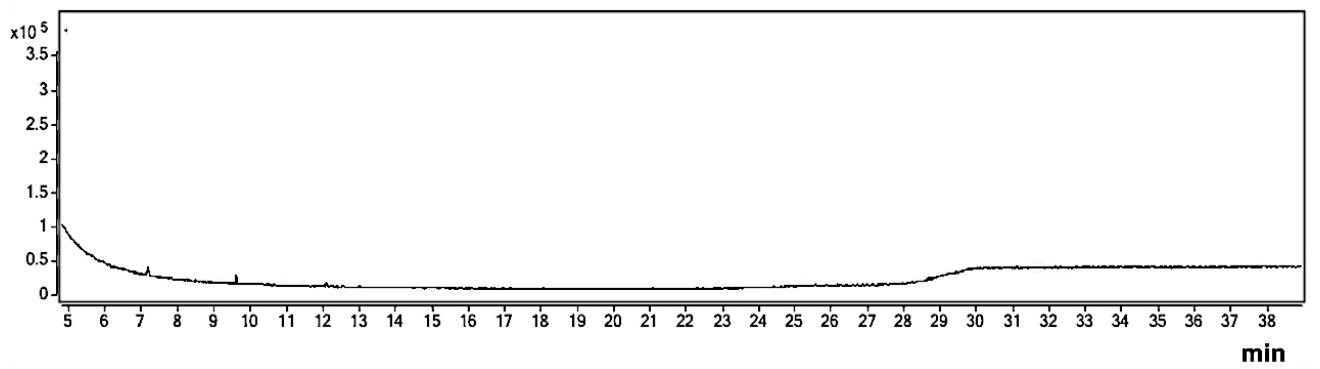

Figure 2. The chromatogram of semi-volatile substances

ISSN 2308-8303 (Print) / 2518-1548 (Online)

Non-volatile organic compounds leached from the primary packaging were determined by HPLC using two detectors – UV and a mass-selective detector. This method is generally accepted for such studies [2]. The results obtained by HPLC/UV/MS were evaluated using two reference standards depending on the ionization mode (positive or negative).

When examining the sample by HPLC/UV/MS at the 0.42 min point, a compound with a concentration of 42.4 μg mL^{-1} was detected, which was higher than the AET value of 5 μg/mL we calculated (**Figure 3***C*).

According to the mass spectrum in the positive ESI mode, the compound was identified as a derivative of the API – hyaluronic acid, so the source of its entry into the implant is not leaching. Therefore, this impurity was not considered by us among the substances leached/extracted from the primary packaging.

Metal impurities

Among the metals potentially leachable from the primary packaging, all metals listed in **Table 1** above were evaluated. The results obtained using the ISP/MS method were evaluated against reference standards for the tested metals. The MS peaks were compared with the MS library for GC and with the known MS templates for LC to identify the detected compounds. Only one metal, lithium (Li), was detected by

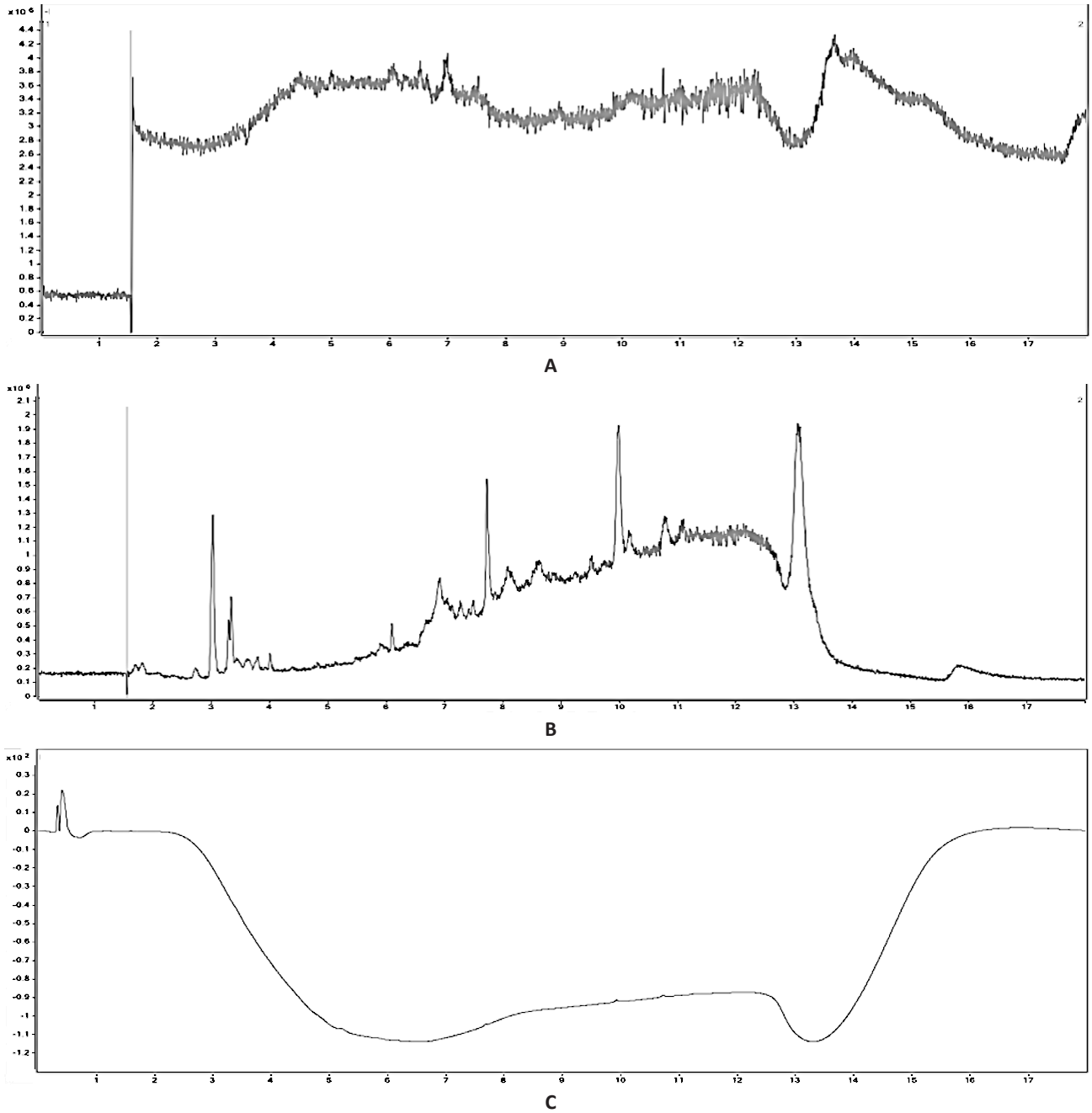

Figure 3. The HPLC chromatogram of the solution studied: **A** – HPLC/MS, negative ionization, **B** – HPLC/MS, positive ionization, **C** – HPLC/UV

the ISP/MS method at a level exceeding the expected acceptable level (0.005 μg L^{-1} after 50-fold dilution). However, Li at such trace levels has no toxicological or biological effect.

The borosilicate glass used to manufacture the syringe cylinders for gel storage contains not only silicon and boron but also alkali metals, such as sodium, potassium, and lithium, at low concentrations. Lithium oxide (Li_2O) is added to the glass to increase thermal resistance, reduce the coefficient of thermal expansion, and improve chemical durability. A portion of these ions may leach into the solution during prolonged contact, especially if the medium has a particular ionic strength, pH, or viscosity that promotes diffusion.

The presence of low concentrations of unknown extractables was considered acceptable.

■ Conclusions

This article presents the algorithm and results of a study on substances leached from the primary packaging of injectable implants containing stabilized hyaluronic acid. Only one unknown organic compound was detected by the HPLC/UV/MS analytical method. However, the peak was studied in the ESI-positive mode and was identified as a compound related to hyaluronic acid; therefore, this substance was not considered as a substance leached from the primary packaging. Other organic compounds in quantities above the AET were found in the gel samples of the medical device, obtained after evaluating its stability under the conditions specified by the manufacturer in the primary packaging. The ICP/MS method detected a small amount of lithium; however, this substance does not pose a concern due to its insignificant risk to human safety and its low concentration in the sample.

The results of the study demonstrate the confirmation of the quality and safety of the use of medical devices – injectable hyaluronic acid-based implants for the patient under the conditions specified by the manufacturer in the selected primary packaging.

■ References

1. Bondarets, I.; Sidorenko, L.; Antonenko, O.; Lebed, S.; Georgiyants, V. An approach to the technological process validation of manufacturing medical devices using the example of injectable implants based on hyaluronic acid. *Sci. Rise Pharm. Sci.* **2024**, *6* (52), 111–123. https://doi.org/10.15587/2519-4852.2024.319456.
2. Li, J.; Sobańtka, A. A systematic analysis of the effect of extraction solvents on the chemical composition of extraction solutions and the analytical implications in extractables and leachables studies. *J. Pharm. Biomed. Anal.* **2023**, *222*, 115081. https://doi.org/10.1016/j.jpba.2022.115081.
3. Bondarets, I.; Sidorenko, L.; Georgiyants, V.; Mishchenko, V. Regulatory and risk-oriented approach to the design and development of medical devices in accordance with Ukraine regulations. *Pharmacia* **2022**, *69* (2), 493–500. https://doi.org/10.3897/pharmacia.69.e82316.
4. Regulation (EU) 2017/745 of the European Parliament and of the Council. 2017. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02017R0745-20250110 (accessed June 8, 2025).
5. Kumaravel, T. S.; Sathya, T. N.; Balaje, R.; Pradeepa, P.; Yogaraj, D.; Murali, M. R.; Navaneethakrishnan, K. R.; Murugan, S.; Jha, A. N. Genotoxicity evaluation of medical devices: A regulatory perspective. *Mutation Research/Reviews in Mutation Research* **2022,** *789*, 108407. https://doi.org/10.1016/j.mrrev.2021.108407.
6. Bello, W.; Pezzatti, J.; Rudaz, S.; Sadeghipour, F. Study of leachable compounds in hospital pharmacy-compounded prefilled syringes, infusion bags and vials. *J. Pharm. Sci.* **2024,** *113* (11), 3227–3237. https://doi.org/10.1016/j.xphs.2024.08.004.
7. Gusain, A. S.; Chandra, S.; Araújo, I. M.; de Lima, J. P. M.; Coutinho, H. D. M. Scientifically Supported Best Practices in Leachable Screening Studies for Pharmaceutical and Parenteral Drug Products. *Future Pharmacol.* **2025**, *5*, 18. https://doi.org/10.3390/futurepharmacol5020018.
8. Satori, C. P.; Christensen, C. D.; Street, S. M.; Giffin, M.; Pohl, C. M.; Christian, W. V. The analytical evaluation threshold for inorganic metal extractables and leachables analysis of medical devices. *Regul. Toxicol. Pharm.* **2024,** *154*, 105725. https://doi.org/10.1016/j.yrtph.2024.105725.
9. Sündermann, J.; Bitsch, A.; Kellner, R.; Doll, T. Is read-across for chemicals comparable to medical device equivalence and where to use it for conformity assessment? *Regul. Toxicol. Pharm.* **2024,** *149*, 105622. https://doi.org/10.1016/j.yrtph.2024.105622.
10. Armstrong, B. L.; Senyurt, A. F.; Narayan, V.; Wang, X.; Alquier, L.; Vas, G. Stir bar sorptive extraction combined with GC–MS/MS for determination of low level leachable components from implantable medical devices. *J. Pharm. Biomed. Anal.* **2013,** *74*, 162–170. https://doi.org/10.1016/j.jpba.2012.10.019.
11. Goud, N. S., Chapter 34 – Biocompatibility Evaluation of Medical Devices. In *A Comprehensive Guide to Toxicology in Nonclinical Drug Development (Third Edition)*, Faqi, A. S., Ed. Academic Press: 2024; pp 957–973. https://doi.org/10.1016/B978-0-323-85704-8.00030-X.
12. Acosta, M.; Bizzoco, L.; Boiocchi, C.; Gobbi, A., Use of New Formulation in Hyaluronic Acid in Regenerative Medicine. In *Regenerative Medicine in Sports and Orthopaedics: A New Approach*, Gobbi, A.; Nakamura, N.; Lane, J. G.; Dallo, I., Eds. Springer Nature Switzerland: Cham, 2025; pp 315–324. https://doi.org/10.1007/978-3-031-84693-9_23.
13. Gao, E. Y.; Tan, B. K. J.; Teo, J. Y. Y.; He, G. S.; Tan, C. J.-W.; Yeo, B. S. Y.; Chua, A. J. K. Hyaluronic Acid for Sinonasal Surgery: A Systematic Review and Meta-Analysis. *International Forum of Allergy & Rhinology* **2025,** *15* (6), 616–625. https://doi.org/10.1002/alr.23537.
14. Muhammad, S.; Syed Wasif Ali, S.; Muhammad Abdul, S. Efficacy of Intraarticular Hyaluronic acid and Cortico- Steroid Co-Injection versus Hyaluronic acid in Knee Osteoarthritis. *Proceedings S.Z.M.C* **2024,** *38* (4), 285–289. https://doi.org/10.47489/szmc.v38i4.638.
15. Torkaman, G.; Rostami-Mehr, E.; Bayat, N.; Mofid, M. Comparing the impact of hyaluronic acid injections and exercise therapy alone and combined on the postural sway and base of support in individuals with knee osteoarthritis: a quasi-experimental study. *International Journal of Therapy and Rehabilitation* **2025,** *32* (4), 1–17. https://doi.org/10.12968/ijtr.2024.0086.
16. United States Pharmacopeia. General Chapter ⟨1664⟩ Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems; *United States Pharmacopeia (USP–NF)*: Rockville, MD, **2022**. https://www.usp.org.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

17. Tanaka, M. L.; Saylor, D. M.; Elder, R. M. Polymer-interface-tissue model to estimate leachable release from medical devices. *Mathematical Medicine and Biology: A Journal of the IMA* **2024,** *41* (4), 382–403. https://doi.org/10.1093/imammb/dqae020.
18. Saadati, F.; Bahrulolum, H.; Talebi, M.; Karimi, M.; Bozorgchami, N.; Ghale, R. A.; Zafar, S.; Aghighi, Y.; Asiaei, E.; Tabandeh, F. Advances and principles of hyaluronic acid production, extraction, purification, and its applications: A review. *Int. J. Biol. Macromol.* **2025,** *312*, 143839. https://doi.org/10.1016/j.ijbiomac.2025.143839.
19. Kostadinova, T.; Trittler, R.; Hoppe, R.; Hug, M. J. 3PC-026 Leachables in syringes containing ethanol, propofol or mRNA vaccine. *European Journal of Hospital Pharmacy* **2025,** *32* (Suppl 1), A29. https://doi.org/10.1136/ejhpharm-2025-eahp.58.
20. Chandra, G. V.; Bavisetti, L.; Anantam, K. Method Development and Method Validation of Volatile Leachables Amount for Oncology Drug Product Injection by Headspace Gas Chromatography Mass Spectrometry Technique. *Res. J. Chem. Environ.* **2025**, *29* (5), 118–127. https://doi.org/10.25303/295rjce1180127.

Information about the authors:
Inna R. Bondarets (*corresponding author*), Ph.D. Student, Department of Pharmaceutical Chemistry, National University of Pharmacy (Kharkiv, Ukraine); https://orcid.org/0009-0004-0286-3966; e-mail for correspondence: rud-i@ukr.net.
Victoriya A. Georgiyants, Dr.Sci. in Pharmacy, Professor, Head of the Department of Pharmaceutical Chemistry, National University of Pharmacy (Kharkiv, Ukraine); https://orcid.org/0000-0001-8794-8010.