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In situ gels as a modern method of intranasal vaccine delivery

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The continuous emergence of new pathogens and the evolution of microbial drug resistance make it absolutely necessary to develop innovative, effective vaccination strategies. Use of nasal vaccination can increase convenience, safety, cause both local and systemic immune reactions. Intranasal administration nevertheless has a number of shortcomings that can be overcome by using the latest achievements of pharmaceutical science. One of the aspects of such solution may be the use of systems for the production of intranasal vaccines *in situ* – polymer compositions that provide a directed sol-gel transition controlled by the physiological conditions of the nasal cavity. At the same time, the gelation of the administered dose in contact with the nasal mucosa involves prolonged exposure of the drug at the injection site, greater mucoadhesion, counteraction to mucociliary clearance, modified and more complete release. A number of both foreign and domestic manufacturers produces polymers such as chitosan, gums, polyoxyethylene and polyoxypropylene block copolymers (poloxamers, proxanols), carbomers. For effective pharmaceutical development of new intranasal IBD delivery systems corresponding to the QbD concept, not only the knowledge of the range of excipients is necessary, but also simple, accessible, and reproducible methods for determining indicators that define the critical parameters of such delivery systems. In accordance with the conducted scientific search, the main indicators of standardization of *in situ* intranasal systems were identified: temperature and time of gel formation, gel strength, rheological characteristics, mucoadhesion, release, nasal mucociliary clearance time.

Keywords: *in situ gelation; immunobiological drugs; intranasal vaccines; chitosan; gums; poloxamers*

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In situ гели как современный способ интраназальной доставки вакцин

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Непрерывное появление новых патогенов и эволюция устойчивости микроорганизмов к препаратам делают абсолютно необходимой разработку инновационных эффективных стратегий вакцинации. Использование назальной вакцинации может повысить удобство и безопасность, вызвать как местные, так и системные иммунные реакции. Интраназальное введение тем не менее обладает рядом проблем, решение которых возможно с использованием последних достижений фармацевтической науки. Одним из аспектов может быть использование для производства интраназальных вакцин *in situ* систем – полимерных композиций, обеспечивающих направленный, контролируемый физиологическими условиями носовой полости переход «золь – гель». При этом гелеобразование вводимой дозы при соприкосновении со слизистой носовой полости предполагает длительную экспозицию лекарства на месте введения, большую мукоадгезию, противодействие мукоцилиарному клиренсу, модифицированное и более полное высвобождение. Такие полимеры, как хитозан, камеди, блок-сополимеры полиоксиэтилен и полиоксипропилен (полоксамеры, проксанолы), карбомеры, выпускаются рядом как иностранных, так и отечественных производителей. Для эффективного проведения фармацевтической разработки новых интраназальных систем доставки иммунобиологических препаратов, соответствующих концепции QbD, необходимы не только знания ассортимента вспомогательных веществ, но и простые, доступные, воспроизводимые методики определения показателей критических параметров подобных систем доставки. В соответствии с проведённым научным поиском были выделены основные показатели стандартизации *in situ* интраназальных систем: температура и время гелеобразования, прочность геля, реологические характеристики, мукоадгезия, высвобождение, время назального мукоцилиарного клиренса.

Ключевые слова: *in situ гелеобразование; иммунобиологические препараты; интраназальные вакцины; хитозан; камеди; полоксамеры*

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Introduction

The most effective methods of prevention and treatment of infectious diseases are vaccination and immunobiological drugs (IBD). Notably, vaccines delivered intranasally have the capacity to induce immunity of the mucous membrane, tissues of which contain both antigen-presenting cells and antigen-processing cells capable of initiating cell-mediated immune responses, including immunological memory. Nasal vaccines can also induce systemic immunity through the mucosal immune system [1].

Intranasal vaccination was first mentioned in the article of the Soviet scientist Kh.M. Rosenberg in 1954 in the PubMed database of medical publications [2]. The first IBD used intranasally in living organisms is the BCG vaccine for tuberculosis [3].

The recently developed approach holding a lot of promise for development of vaccines employs VLPs (virus-like particles), which are made up of specific viral proteins and are spontaneously assembled into configurations imitating the conformational structure of viruses, but without viral genes. Intranasal vaccination with VLPs for prevention of

influenza induces higher levels of cross-reactive IgA and IgG antibodies than parenteral vaccination. The preclinical studies have demonstrated that such vaccines tend to enhance both humoral and cell-mediated immune responses.

Currently, there are intranasal vaccines that have been approved or are being evaluated through clinical trials in Russia (Gam-COVID-Vac, VLP-Corona), the United States (AdCOVID, MV-014-212) and countries of the European Union (COVI-VAC, ChAdOx1-S). Vaccines injected intramuscularly are intended for inducing humoral and cell-mediated immune responses. However, they provide poor protection against replication of the virus in the upper respiratory tract due to the absence of the local IgA (sIgA) antibody immune response. At the moment, a number of new nasal vaccines against COVID-19 are being developed; the preclinical studies and clinical trials have demonstrated high-level production of neutralizing antibodies and IgA and T cell-mediated responses of mucous membranes.

Intranasal vaccine delivery offers multiple advantages compared to traditional injection routes: absence of invasion, high vascular density in the nasal cavity, capability of the therapeutic agent to reach cerebrospinal fluid, bypassing the blood-brain barrier. The downside of the intranasal route of delivery is mucociliary clearance playing a critical role in prompt removal of foreign substances from the nasal cavity [4]. Another physiological characteristic of the mucous membrane of the nasal cavity – active clearance driven by the coordinated beating of cilia that move foreign items and therapeutic agents trapped in the mucus out of the nose as well as multiple enzymes and specific interferon, which, in its turn, protects the body against pathogens, add up the complexity of intranasal vaccination [5]. However, these problems can be solved with the proper composition of additives to increase adhesion of the therapeutic agent on the mucous membrane and improve its full penetration into the systemic circulation [6]. Using of *in situ* delivery systems is one of the ways to solve the problems associated with intranasal IBD delivery.

In situ systems based on smart polymers are advanced systems for controlled delivery, which undergo phase changes in response to specific stimuli at the intended absorption site (the pH value, presence of specific ions, moisture, etc.).

Thus, the **purpose** of this study can be defined as a review of specific features and main aspects of pharmaceutical development of *in situ* systems for intranasal delivery of IMD.

In situ templates for intranasal vaccine delivery

A variety of polymers with different mechanisms of gelation and phase transition stimuli are used for development of *in situ* systems. These polymers can be natural (chitosan, pectin, gums) and synthetic (poloxamers, carbopols, polyvinyl alcohol, etc.).

The analysis of the PubMed database of medical publications for the 2000–2022 timespan, using such keywords as intranasal *in situ* vaccine, intranasal *in situ* peptide, intranasal *in situ* protein, was used to estimate the usage frequency for different polymers in development of *in situ* IBD delivery systems (**Figure**). Natural polymers – chitosan (35%) and various gums (16%) as well as synthetic poloxamers (19%) were most popular. The main characteristics of polymers are discussed below.

Chitosan is a naturally occurring bio-polysaccharide of cationic nature. Its mucoadhesion can be explained by the electrostatic interaction between its positively charged cationic molecule and negatively charged mucin [7–20].

Polyanions and polycations (such as chitosan) are characterized by the capacity for multipoint cooperative interaction with immunocompetent cells and can be seen as prospective immunomodulators [21].

Poloxamers are a class of nonionic triblock copolymers [9, 10, 15–17, 22, 23]. Poloxamers 188, 407, 124 are most frequently used in pharmaceutical IBD technology.

The studies of poloxamer 407 aqueous solutions demonstrated the occurrence of an *in situ* sol-gel transition at increased temperatures due to reduction in intermolecular interactions [24].

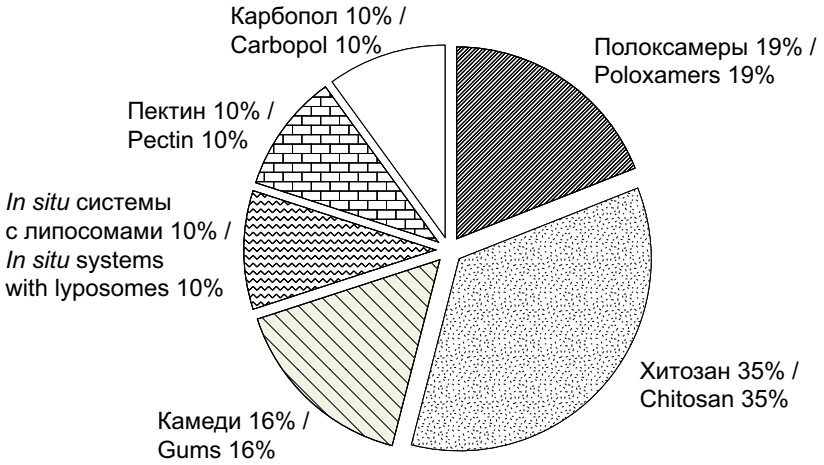

Figure. Polymer usage ratio based on analysis of the medical publications database PubMed.

Рисунок. Соотношение использования полимеров на основе анализа базы данных медицинских публикаций PubMed.

Poloxamer 188 is a safe biocompatible polymer, which can be used in the protein drug delivery system [25]. The pharmacological activity of poloxamer 188 has been extensively studied in the last ten years; it has been proved that it can be used in treatment of sickle cell disease [26]. Note that poloxamer 188 has hemorheological, antithrombic, anti-inflammatory properties, which are being extensively studied at present [27].

Among the above-mentioned triblock copolymers, poloxamer 124 can be used as a solubilizer, plasticizer and emulsifier; however, its *in vivo* pharmacokinetic properties are still unclear [28, 29].

As noted previously, poloxamer 407 is the main thermosensitive ingredient. Moreover, other excipients added to the complex that contains poloxamer 407 can be used to regulate the temperature of the phase transition and to increase the stability of the composition and to improve the biopharmaceutical properties [30].

Currently, a poloxamer 188 analog is manufactured in Russia, but no commercially manufactured alternative to the thermosensitive poloxamer 406 has been available so far [31, 32].

Three kinds of *gums* – gellan, xanthan and guar – have been studied as prospective components of *in situ* systems [33–37]. Gums used in such systems are responsible for ion-selective phase transition [38].

Gellan gum is an extracellular water-soluble anionic polysaccharide produced by bacteria Sphingomonas elodea [39].

Guar gum is a galactomannan polysaccharide extracted from guar beans.

Xanthan gum is a natural polysaccharide produced by fermentation of the gram-negative bacterium *Xanthomonas campestris*.

Pectin is an anionic biopolymer widely used in the food industry [40–42]. Natural pectin has anti-carcinogenic properties and can suppress colon cancer [43]. Largest manufacturers and markets for food and pharmaceutical pectin are concentrated in Europe, South America, China, and Iran. Currently, there is no commercial production of pectin in Russia [44].

Carbomers are high-molecular-weight crosslinked polyacrylic acid polymers [23, 45]. In healthcare practice, aqueous solutions of carbomers are used vaginally as a spermicide that protects against HIV infection and possibly other sexually transmitted diseases [46].

Development of intranasal *in situ* delivery systems for immunobiological drugs

The main disadvantage of regular nasal gels is the lack of dose precision; patients complain of the sensation of a foreign body in their nose. Addressing the problems, scientists from the Chinese University of Hong Kong have developed a thermoreversible *in situ* gel for intranasal delivery of the DB213 inhibitor of HIV-1 replication, using a combination of poloxamers 407, 188 and chitosan [16].

One of the first studies of intranasal *in situ* IBD delivery, including the *in vivo* testing of the formulation, was performed by Indian scientists Shailja et al. who developed a liposome *in situ* gelling system for delivery of hepatitis B vaccine [47]. The liposome medium was prepared from egg lecithin and cholesterol, while the polyacrylic acid served as an *in situ* polymer. The *in vitro* measurements showed that 54% of the drug was released, though the *in vivo* studies revealed excellent mucoadhesive properties of the formulation.

In 2020, Bedford et al. developed an *in situ* vaccine against influenza, using chitosan and poloxamers 188 and 407 as polymers responsible for its *in situ* properties [10]. The improved mucoadhesion achieved, in the authors' opinion, by using chitosan was proved both *in vitro* and in *in vivo* tests.

U.S. researchers developed a GelVac® dry powder norovirus vaccine [40, 41]. The inactivated H5N1 influenza vaccine based on the GelVac® nasal powder formulation was approved by FDA (U.S. Food and Drug Administration) for clinical trials involving people. The tests using guinea pigs demonstrated enhanced and longer immunization compared to the non-*in situ* vaccines. The immune response resulted from the increased IgA levels in blood; the enzyme-linked immunosorbent assay (ELISA) was used for measurement of IgG1 and IgG2 subclass antibodies in pooled serum samples from each group.

At the Gamaleya National Research Center of Epidemiology and Microbiology of the Health Ministry of Russia, researchers tested the adjuvant for the VLP-based vaccine for intranasal administration to prevent COVID-19. The adjuvant consisted of the gel resulting from the mixture of gellan gum 0.5 and 2% poloxamer 124 diluted in distilled water with addition of 15% PBS (phosphate buffered saline). The trial tests showed that the gel demonstrated a high retention rate in the nasal cavity – up to 83%. The group of hACE2 AC70 mice intranasally immunized with the VLP-based vaccine containing 80 μg of the antigen per dose and the above adjuvant in the ratio 3 : 2 demonstrated the enhanced T cell-mediated immune response manifested in a statistically significant increase in the specific proliferation index (3.3 ± 0.28) in the blastogenic lymphocyte response, which correlated with production of interferon-γ secreting cells. After the animals had been infected with SARS-CoV-2, half of the animals who were vaccinated intranasally with three doses of the vaccine survived, while in the control group of animals who were not vaccinated all the animals died. The safety of gel was assessed and confirmed. The three-dose intranasal immunization with the VLP-based vaccine with gel adjuvant had no effect on the body mass index and body weight gain during 42 days of the experiment. The food and water consumption levels in the group of immunized animals were higher compared to the control group.

The autopsy examination of hACE2 AC70 mice on the 7th day after the second and third immunization, including visual examination of the exterior body condition, internal organs and tissues, cranial cavity, thoracic, abdominal and pelvic cavities, skeleton and musculoskeletal system did not reveal any gross changes associated with the effect of the vaccine containing an adjuvant.

Undoubtedly, the composition of gels used for intranasal vaccines needs to be further improved to optimize the formulations and enhance the protective effect of vaccines.

Design of pharmaceutical development of *in situ* intranasal immunobiological drugs

The most fundamental achievement of present-day research and development (R&D) in the pharmaceutical technology and biotechnology is optimization and standardization of the pharmaceutical development process [48, 49]. One of the most widely used methods is construction of a design space. Such methods are actively used in development of solid pharmaceutical forms (Harrington's desirability function, SeDeM expert system) [50, 51] and are documented in ICH Q8.

Thus, with all present-day options that can be used to ramp up R&D processes, researchers have two *main tasks*: the well-grounded choice of a pool of auxiliary substances used in development and critical parameters for the specific system as well as reproducible available methods offering the reliability of the obtained results.

Selection of excipients for developing new *in situ* intranasal IBD delivery systems can be based on scientific and patent search (Figure). The evaluation of effectiveness and survivability of immunobiological substances is an essential part of IBD pharmaceutical development [52].

Selection of critical parameters for *in situ* intranasal delivery systems: temperature and gelation time, rheological parameters, *in vitro* release, *in vitro / ex vivo* mucoadhesion, *in vivo* control of mucociliary clearance [6].

Most of the researchers use the method offered by Gilbert et al. in 1987 to measure *the gelation temperature* [53].

Similar methods are used to measure *gelation time* and *gel strength*, which are critical for assessment of the mucociliary clearance and its reduction [10, 11, 16–18, 22, 23, 54].

Testers with vertical diffusion cells known as Franz cells are often used for evaluation of the IBD *release* profile in formulations [4, 8, 9, 24, 34].

To measure *in vitro* the *mucoadhesive strength* of polymeric compositions after the *in situ* gelation in the nasal cavity, Canadian scientists from McMaster University offered to calculate the mucoadhesive strength by constructing a calibration curve, the relationship of the tensile strength and the end position of plates with 2% mucin solution and the composition of the tested polymers [13].

To enhance the precision of screening, some researchers measure the nasal mucociliary clearance time following the method offered by Zaki et al. in 2007 [55].

Conclusion

In situ systems for intranasal vaccine delivery makes it possible to achieve both local and systemic effect of IBD without skin penetration. Vast experience has been gained in R&D processes, preclinical and clinical studies of such systems used for delivery of protein and other particles. The scientific literature search has shown that thermoreversible compositions of polymers are the most popular solution for intranasal *in situ* IBD delivery, and ion-selective polymers can be an excellent alternative for further research and development of new *in situ* systems of intranasal delivery.

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