Section 2. Pharmaceutical sciences

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MAIN PROBLEMS IN THE PHARMACEUTICAL DEVELOPMENT AND MANUFACTURE OF DRUGS ON THE BASIS OF IN SITU SYSTEMS

Abstract. *In situ* systems are one of the most promising modern delivery systems. Their use in clinical practice can solve the problems of patient compliance, as well as increase the bioavailability of active ingredients, However, the global scientific community needs to make efforts to solve the key problems that stop the development of the technology of these targeted delivery systems.

Keywords: *in situ* systems, *in situ* gelling, implants, drug design, target delivery system.

Introduction. According to an analysis of the database of medical publications PubMed [1–5], *in situ* systems are one of the most dynamically developing area in drug design. *In situ* systems show high potential and clear advantages over classical drugs in *in vitro, in silico* and *in vivo* trials [2; 3]. However, the number of registered and industrially produced drugs based on them is still insignificant [4; 5].

Despite sufficient accumulated clinical experience, drug design *in situ* systems remains more scientifically oriented and often does not go beyond scaling.

More and more *in situ* systems with proven efficacy are registered as medical devices and cosmetics, which no longer allows them to be considered as targeted drug delivery systems. In order to form a strategy for solving this problem, it is necessary to determine the causes of this phenomenon.

The purpose of this work is to consider the main problems both in the field of pharmaceutical development and the introduction of in situ systems into clinical practice and the industrial production of drugs based on them.

The first reason is the conservatism in the consumer preferences of patients in terms of medicines and the relative freedom for perfumes and cosmetics. Patient confidence in medications and routes of administration that have been marketed for years, despite obvious shortcomings, is a major reason for the slow pace of innovation in treatment regimens.

One such example is the use of eye drops in ophthalmic practice. Despite the fact that dozens of studies have shown the problems associated with the use of eye drops, this dosage form continues to be the most popular and widely used in ophthalmology.

When a patient instills eye drops, a high percentage of errors are allowed, which lead to a significant loss of dose, and, accordingly, can lead to ineffectiveness of the therapy. Using classic eye dropper bottles, the risks of cross-microbial contamination are increased (by some researchers, these risks are

estimated as comparable or even greater compared to applying the drug by a patient with a finger – as for contact lenses, eye films, gels, etc.). Leakage of eye drops from the lacrimal sac occurs even when instilled by medical personnel. the dose of eye drops is measured using the dropper of the package, which in itself cannot provide absolute accuracy. dosing accuracy for such dosage forms is extremely conditional.

At the same time, in the form of eye drops, not only drugs are produced that have a local effect on the cornea – for example, containing hyaluronic acid or carbomer – for the treatment of dry eye syndrome, but also drugs containing active ingredients with a pronounced pharmacological effect – adrenoblockers, adrenomimetics, M-anticholinergics and others, for which dosing accuracy will be the property that determines the effectiveness of pharmacotherapy.

An alternative to classic eye drops are in situ ophthalmic systems – with a reduced risk of leakage, a prolonged effect, which reduces both the frequency of use and the likelihood of errors with each instillation. However, despite all the significant advantages, such systems not only have not yet replaced the classic eye drops in treatment regimens, but are also present on the pharmaceutical market in extremely limited quantities.

The solution to this problem may be to conduct international campaigns to educate patients in the field of in situ systems – to increase their level of awareness and the possibility of choosing alternative effective treatments.

In the sphere of perfumery and cosmetic products, unlike most dosage forms, consumer awareness of the benefits of new systems is carried out through well-established marketing strategies. On the one hand, this explains the reason for the registration of some targeted in situ delivery systems as cosmetics.

Medical devices are mainly intended for manipulation by medical personnel. Since the global practice includes a streamlined process of continuous education of doctors and medical personnel, informing about new effective targeted delivery systems that would not only increase the effectiveness of therapy and patient adherence, but also facilitate medical manipulations, occurs quite quickly and in a timely manner. The publication of a large number of review articles intended for professionals in this field, the holding of thematic conferences and congresses, trainings, master classes and webinars, contributes to the fact that doctors and medical staff demonstrate a much greater commitment to the use of new delivery systems in therapy than patients.

The main reason hindering the introduction of in situ systems into clinical practice is the insufficiency of the regulatory framework for registration and standardization of such drugs.

It is obvious that registration of such systems only in the initial or final form ("before" or "after" the phase transition) is an incorrect approach, leading to the appearance on the market of ineffective or low-quality drugs that discredit delivery systems in general.

Standardization of in situ systems should be a two-step process, and include both traditional quality measures related to the aggregate state of the system or route of administration (e.g., viscosity, pH, isoosmoticity) and specific quality indicators that are important to control during the screening step (e.g., time film formation, strength of the gel structure, mucoadhesion, film elasticity, gas permeability, etc.). the phase transition process is separately standardized and studied depending on the factors initiating it. Thus, for thermoreversible systems, the most important parameter of the phase transition is the temperature of gelation, for ion-selective polymers, the ionic composition, etc. These characteristics help the researcher to predict the targeting of the in vivo delivery system even at the drug design level. The study of the parameters that determine the phase transition is complicated by the actual lack of simple and accessible validated models. Most researchers still use in vivo and ex vivo methods that cannot be sufficiently reproducible and experimentally controlled. As an alternative, biorelevant in vitro reproducible models should be proposed, but the modern scientific community is just beginning

to deal with the issues of their construction. Models of the vitreous body have been developed to assess the phase transition and the formation of in situ implants, the nasal cavity – to develop intranasal in situ gels, but their implementation in drug design and validation is still a matter for future research.

There are certain prospects for the introduction of modern 3D printing technologies for modeling in vitro systems. This method would provide standard models commercially available to many research laboratories – and would facilitate harmonization of in situ system evaluation parameters.

The third, but no less important problem among others, limiting the introduction of in situ systems into production, is the stability of the above indicators. Thus, recent studies have shown that some thermoreversible matrices based on poloxamer 407, which provide a phase transition during development in an acceptable temperature range, lose this property during long-term storage, due to which the gelation temperature drops to room values that do not correspond to the tasks research. To stabilize this parameter, various technological methods can be proposed, in particular, in recent studies, the range of excipients introduced into the composition of thermoreversing matrices that stabilize the phase transition temperature has been determined.

However, this circumstance indicates the need to fix at the regulatory level, to conduct long-term technological tests for the developed systems, since the complexity and sensitivity of the phase transition parameters can often make them unstable, inefficient and reduce or even completely eliminate their targeting.

Conclusion. *In situ* systems are one of the most promising modern delivery systems. Their use in clinical practice can solve the problems of patient compliance, as well as increase the bioavailability of active ingredients, However, the global scientific community needs to make efforts to solve the key problems that stop the development of the technology of these targeted delivery systems.

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