Nanomedicine and Drug Delivery Strategies for Theranostics Applications

A. V. Ermakov, E. V. Lengert, S. B. Venig

Alexey V. Ermakov, https://orcid.org/0000-0001-8105-5932, Saratov State University, 83 Astrakhanskaya St., Saratov 410012, Russia, ermakov.ssu@gmail.com

Ekaterina V. Lengert, https://orcid.org/0000-0002-6447-2811, Saratov State University, 83 Astrakhanskaya St., Saratov 410012, Russia, lengertkatrin@mail.ru

Sergey B. Venig, https://orcid.org/0000-0002-4759-5828, Saratov State University, 83 Astrakhanskaya St., Saratov 410012, Russia, sergey.venig@gmail.com

Background and Objectives: Nanomedicine and drug delivery systems are a relatively new but rapidly developing branch of science, which investigate materials in the nano- and microscale range as diagnostic tools or carrier for delivery of therapeutic agents to specific targets within the body in a controlled manner. As far as the systemic administration faces a range of problems that cannot be solved by traditional approaches, it becomes extremely relevant to develop novel therapeutic options. **Results:** In this paper we provided information about the most interesting and promising strategies from our point of view that optimize the drug delivery process using various compositions of nano- and microcarriers of different nature and design, special physicochemical amplifiers, various devices, and methods. The current review briefly presents the latest advances in the field of nanomedicine and drug delivery systems driven by impressive recent results in the field of nanomaterials, drug carriers of different compositions, specific physicochemical amplifiers, various devices and methods. Few basic routes for drug delivery *in vivo* including injections, implantation and transdermal delivery open up a new avenue for an improved topical medical treatment which is considered and compared to each other in the current review. All of these routes offer certain advantages of terms drug absorption, targeting, prolongation, spatiotemporal accuracy, reduction of dosage and many others that must be taken into account to provide a correct approach for the treatment of a specific disease. **Conclusion:** Invasive and non-invasive implantation of drug delivery carriers and devices are reviewed together with transdermal routes leading to effective absorption of drugs with minimal side effects. The innovative approaches to drug delivery discussed here open venue for effective treatment of a wide range of diseases, especially chronic ones, that cannot be defeated by traditional approaches. Although transdermal delivery offers a promising non-invasive way to treat a variety of diseases, chronic illnesses can be treated more effectively by implantation of drug delivery devices with a bidirectional connection that in the future can drastically improve the quality of life. Diversity of emerging technologies in microelectronics, sensors and biomaterials leads to dramatic changes in the medical industry and appearance of new systems providing medical treatment in theranostics fashion.

Key words: nanomedicine, drug delivery, theranostics, implantation, transdermal system.

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Introduction

Currently, a great amount of highly effective drugs is developed, however, the problem of their targeted delivery to a specific organ or pathological site remains challenging. In this regard, one of the main trends in pharmaceutical industries along with the development of novel active biological compounds is the improvement of their delivery into the body. There are several routes for drug delivery based on carriers, which can be introduced into the body by means of injections, implantation or transdermal delivery.

The problems associated with standard injections are caused by difficulties in use by untrained users as syringes can result in injuries and infections and pains. Besides syringes can be reused by people with drug addiction, if they are not disposed properly. A large percentage of patients are afraid of syringes that causes problems in therapy, regardless of the reasons in pain and necessity of use. In order to overcome issues associated with user compliance, a number of needleless syringe designs have been proposed. Such syringes deliver the drug to the subject by injecting the drug through the skin of the subject under air pressure.

However, these techniques do not resolve a range of problems associated with the systemic administration of drugs leading to side effects and the necessity to repeat the procedure regularly. Novel technologies in drug delivery systems offer a range of routes the drug can be delivered in, accompanied by an opportunity to endow it with a bidirectional connection in a theranostics fashion. These systems are based on drug carriers and enable to control release profiles of drugs with high spatiotemporal precision.

The current review is focused on recent advances in the routes of drug delivery and biosensors incorporation into the body. Invasive and non-invasive implantation of drug delivery carriers and devices are reviewed together with transdermal routes leading to effective absorption of drugs with minimal side effects.

1. Delivery of drug carriers by subcutaneous injections

The subcutaneous fat layer is well supplied with blood vessels, therefore, the effect of drugs can be reached with subcutaneous injections are widely employed. Subcutaneously administered drugs be-

come absorbed quickly in comparison to the drugs absorbed via oral administration. Subcutaneous injections are made with a needle at the depth of 15 mm and can provide drug volume of up to 2 mL, which are rapidly absorbed in loose subcutaneous tissue and do not have a harmful effect on it.

A variety of drug delivery carriers were shown to exhibit therapeutic effect in the body upon introduction via subcutaneous injections such as liposomes [1, 2], magnetic iron oxide nanoparticles [3], carbon nanoparticles [4], gold nanoparticles [5] (Fig. 1).

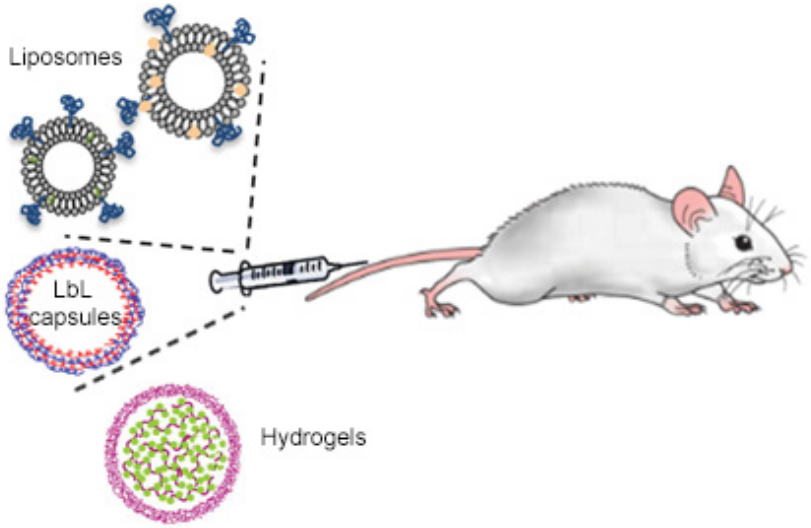

Fig. 1. Different types of drug delivery carriers used in subcutaneous injections. Reprinted with permission from [2]. Copyright Elsevier, 2018

However, it is known that the intravenous administration of liposomes and various polymer-based pharmaceuticals causes vegetative, mucocutaneous and cardiopulmonary reactions in some cases [6]. Symptoms include fever, chills, shortness of breath, hydrops, rash, cough, shortness of breath, polypnea, hypertension/hypotension, and chest and back pains. These symptoms range from mild to severe with an unknown reaction in response to pre-existing allergen-reactive immunoglobulins (e.g., IgE type antibodies). However, modern pharmaceuticals used in clinical practice are not designed to overcome these problems.

The mechanism underlying the reactions to pharmaceuticals in response to intravenous administration is not well understood. It is assumed that the unintentional activation of the complement system, which is the first line of defense of the body against extraneous intrusions, is a causative factor [7].

The authors of [8] have observed an additional problem in the difference of therapeutic effect in dependence on the site of injection. The authors studied the relationship between the left or right ulnar veins and with intravenous contrast injection sites and the quality of improved CT images of the chest. Interestingly, contrast images obtained by injection into the right ulnar vein showed better quality than images obtained by injection through the left arm. An increase in the contrast improved the image quality of a CT scan of the chest when injected into the right ulnar vein, avoiding passage through a possibly squeezed left brachiocephalic vein, that is especially relevant for elderly patients.

2. Implantation of theranostics systems

Biomedical engineering in recent years has made a breakthrough in the field of theranostics materials and devices which are consisted of drug delivery and biosensing systems [9]. These approaches enable tuning of therapeutic treatment employing targeting drugs together with control over release profiles into the body that can increase efficiency in comparison to systemic administration. The drug delivery process can also improve therapeutic affect by targeting a drug to a pathological site. However, this approach demands a mechanism to provide external control over the system at every step of the process. To date, a variety of materials and devices can offer a wide range of mechanisms of drug delivery and release according to the clinical requirements.

Drug delivery approaches can be divided into active and passive. Active systems are designed to implement release in response to an external signal which can be represented by electromagnetic waves, radio waves, ultrasound and others. It means that the system should be composed either of multifunctional composite material or devices containing power batteries and on-board electronics, usually accompanied by sensors. Passive systems designed in a specific way to provide release in response to the physical properties of the medium in the body.

In this way, microfabrication techniques become important in terms of miniaturization of implantable systems to provide implantation of multifunctional theranostics systems to different sites of the body. It should be noted that passive devices are beneficial in terms of size limitations as they are not equipped with active electronic parts and can be introduced to the body in a minimally invasive way [10]. Drug release can be assisted by different types of stimuli such as temperature [11, 12], pH [13, 14], and light [15, 16]. Besides these parameters should be taken into account to provide control over pharmacokinetics and increase therapeutic efficiency although passive systems are unable to implement drug release with complex release profile and dependency on multiple parameters [17].

The drug delivery devices and sensors can be implantable in an invasive and non-invasive way [18] or introduced via the transdermal route [19]. Implantable systems can be represented by complex micron-sized robots [20, 21] or capsules [22, 23]. Usually, implantable devices contain microreservoir filled with a drug, actuator and other electronic components to initialize release, sensors, and antenna to provide bidirectional connection [24]. In the case of active devices, the external transmitter wirelessly receives information from the device and delivers information if the actuating mechanism should be triggered to release the drug. This approach has benefits in comparison to systemic administration as it helps to reduce side effects as released drugs tend to accumulate near the site it was injected in.

In the other case, multifunctional carriers made of composite materials are employed for delivery, detection and release in response to physical and chemical surroundings in the body or specific type of external influence [25]. Biocompatible arrays of free-standing micron-sized chambers made of biodegradable polymers (polylactic acid or polyelectrolytes) were shown to provide either burst release triggered by NIR light [26] or prolonged release in response to enzyme treatment *in vivo* [27]. These chambers allow creating both independent drug depot implants [27] or as functional coating for implants [28]. Besides inorganic fillers, complex films consisted of lipids and biopolymers such as DNA [29] can find application as biosensors.

In dependence on medical indications, the gastrointestinal route for the introduction of sensors and drug delivery systems into the body can be used [22, 23]. This route is beneficial as it is a simple and noninvasive way to introduce drugs, however it is limited by a number of diseases that can be treated. The therapeutic effect of the complex capsule consisted of a camera, illumination, a drug delivery channel and an ultrasound transducer was studied *in vivo*. Once swallowed the capsule provides controllable release in response to pH or enzymatic treatment or in response to an external signal that makes it possible to tune the site of release. In other case composite alginate-based microchambers were studied *in vivo* and shown to be stable in the gastrointestinal tract of C.elegans and release the model drug in response to NIR laser trigger [30].

A wide range of implantable multifunctional systems with a drug depot is represented by composite scaffolds based on functionalized biocompatible polymeric matrices. In combination with the sensing and drug delivery approach, scaffolds are a promising candidate in the field of tissue regeneration [31, 32]. Usually, scaffolds consisted of hydrogels or biopolymers functionalized by drug delivery carriers such as calcium carbonate particles and gelatin microspheres [31, 33]. The basic requirements for tissue engineering implants are biocompatibility, biodegradability, the possibility of cell colonization over the scaffold and cell proliferation in order to form new living tissue, the structure, and functions of which are similar to the properties of native tissue [34]. Along with the restoration of structural defects in tissues, such materials also enable restoration of the functions of the tissues lost as a result of damage [35].

Together with hydrogels, nanofibers have found application as an implantable drug delivery system characterized by high flexibility and prolonged release of anti-glioma drug [36]. Alternatively, «drug delivery» term can suggest also the delivery of light energy as it was demonstrated with an implantable micro-optical semiconductor device, which provides both the delivery of light energy and the detection of optical signals within the body [37].

In general, hydrogels are widely applied as drug delivery carriers and sensors due to the great possibility of functionalization by fillers of differ-

ent nature. Hydrogels functionalized by graphene were shown to have great stimuli-responsiveness with high efficiency as an active component in actuator systems [38]. This approach continues the trend which started since the investigation of the first glucose electrochemical sensor. Together with new developments in the area of biocompatible functional materials, wireless power supplies and bioengineering, the latest advances in sensing techniques allowed investigation of implantable biosensors, that in some cases are accompanied by drug delivery systems in a theranostics fashion.

Graphene applied as a functional component in the hydrogel matrix contributes to the actuation performance of the composite in terms of electrical conductivity and mechanical properties, which allows the resulted material to change shape and dimensions in response to stimuli in a reversible manner. Hydrogels doped with graphene were shown to exhibit stimulus-responsive swelling that allowed realizing signal transduction in biosensors and bioelectronics [39]. In this way, composite hydrogels found a wide range of applications as implantable sensors [40]. Hydrogel based composites were demonstrated to serve as a pH [41] electrical [42] and photonic [43] responsive-actuator.

Along with advances in biocompatible composite materials, new developments in microelectronics, microfluidics, microsensors have led to an increasing number of technologies focused on implantable biodevices for continuous monitoring. These devices can help to resolve many clinical tasks including detecting or monitoring pathogens, ions, diseases, etc. [44]. Progress in this area has led to the development of a wireless implantable glucose/lactate sensing biochip made on the basis of on-chip potentiostats and new signal processing techniques [45]. Implantable bio-micro-electro-mechanical systems for the monitoring of blood flow in situ have also been developed [46].

3. Transdermal delivery of hybrid carriers and methods of stimulation

Various technologies and strategies for the delivery of therapeutic agents into the body have been widely investigated over the past decades. To date, many studies have proven an increase in the delivery efficiency of vaccines and various drugs, that can reduce the dosage of the drug and provide a minimally invasive alternative to traditional vaccination and dosage forms. Significant progress has been made in the field of various vaccinations and transdermal drug delivery among which are the following technologies: jet and powder injections, microneedles, microporation technologies, electroporation, sonoporation, as well as transdermal and transfollicular drug delivery.

Most drugs employed today in clinical practice are either injected or orally administered. Injections usually provide a quick, direct route to the bloodstream, while oral administration involves metabolization of the pharmaceutical agent in the liver. Hepatic metabolism reduces the efficiency of pharmaceutical agents up to 90% in some cases. As a result, a significant amount of the drug does not reach the rest of the body due to the detoxification of the drug by the liver. Despite this drawback, oral administration is still the most preferred route of administration of pharmaceutical drugs due to simple administration and the opportunity to avoid invasive methods such as injections.

To date, sonophoresis becomes an increasingly common method of drug administration. Therapeutics or model substances can penetrate through the skin, hair follicles, and sweat glands by means of vibration influence. The ultrasonic treatment (sonophoresis) is one of the least invasive physical stimulants. It is effectively employed in order to enhance intra- and transdermal delivery of bioactive molecules and solid particles. Ultrasound treatment of the skin at frequencies over 0.7 MHz leads to an increase in pressure in the medium and subsequent formation of cavitation bubbles inside the inherent cavities represented by hair follicle shafts and sweat glands [47]. Vibrations of the bubbles within follicles provokes movement of the particles' suspension down the follicle. Previously, ultrasound treatment at the frequency of 1 MHz and a power density of 2 W/cm^2 was shown to be safe for the skin of rats [48].

Ionophoretic delivery is another effective non-invasive approach for therapeutic drug delivery [49]. Typically, transdermal iontophoresis generates a small electric current (0.1–0.5 mA cm^{-2}) in the skin to induce transdermal molecular transport, enhancing drug delivery by electro-repulsion and electroosmosis. At neutral pH, the skin is negatively charged and has cationic selectivity [50]. Thus, the passage of current causes a convective flow of solvent from the anode to the cathode, leading in increased transfer of cations and improved transdermal transfer of neutral polar substances. The effects of electro-repulsion and electroosmosis depend on the physicochemical and electrical characteristics of the membrane. In addition, the negative charge of the skin can be reduced, neutralized, or even completely altered by the iontophoresis of some cationic, lipophilic species

[51]. In addition, a combined strategy to improve the permeability of the skin for drugs based on the simultaneous use of sonophoresis and iontophoresis was developed. This strategy showed a significantly higher gain in comparison to using only one approach. A miniature device able to induce sonophoresis and iontophoresis is a promising approach due to the enhanced transdermal drug delivery and the possibility of self-administration in the cosmetic and therapeutic fields [52].

Various alternative methods for improved skin penetration are presented in Fig. 2.

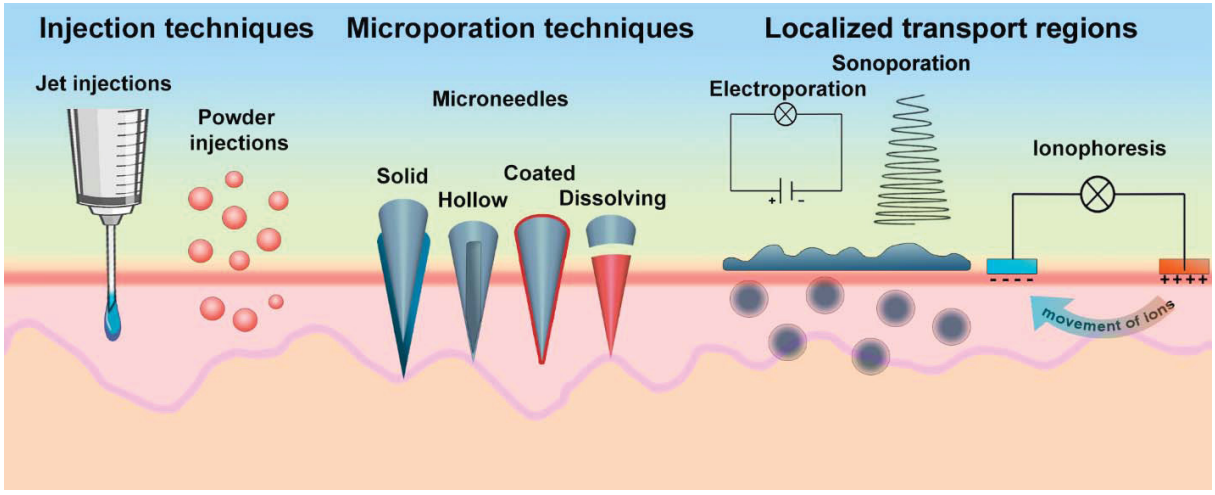

Fig. 2. Different approaches towards subcutaneous drug delivery. Injection, microporation and local transport region (LTR) techniques are displayed in representative dimensions relative to the epidermal layer of the skin

Technologies related to microporation for the delivery of macromolecular drugs, biopharmaceuticals and vaccines are developing rapidly [53].

Microneedle mediated drug delivery has been proposed as a strategy for disrupting the barrier function of the stratum corneum to provide efficient transport of molecules through the skin. This strategy suggests the employment of micron-sized needles of different geometries, which penetrate through the skin and create transitional water channels. Microneedles alone or in combination with other enhancing strategies (chemical or physical) have been shown to significantly increase skin permeability for a variety of therapeutic molecules, including *in vitro*, *ex vivo* or *in vivo* biopharmaceuticals [53].

A device with a microneedle matrix perforates the stratum corneum of the skin, which provides direct access of drugs to the underlying viable epidermis in absence of contact with blood vessels and nerve fibers located in the dermis. To date, there are several different approaches for transdermal drug delivery based on microneedles: solid microneedles (to increase the permeability of drugs by means of microholes created over the skin), microneedles with a coating (to provide quick dissolution of the drug together with the coating at underlying viable epidermis), soluble microneedles (for quick or controlled release of the drug trapped within microneedles), hollow microneedles (used to penetrate through the skin and provide release of liquid drug after infusion or diffusion of the drug through the hole of the needle) [54].

4. Application in medical practice

Currently, several microneedle products were released on the market for cosmetic applications. LiteClear® microneedles are used to treat acne and other skin diseases, and MicroHyala® is used to reduce the appearance of first wrinkles [54]. The only microneedle system available on the market for therapeutic use is the Becton-Dickinson Soluvia® microinjection device, consisting of a 1.5 mm hypodermic needle attached to a syringe pre-filled with an influenza vaccine. Soluvia® is currently marketed worldwide as IDflu®, Intanza®, and Fluzone Intradermal® and applied for intradermal vaccination. Micronjet® is used as an effective, accurate, and almost painless intradermal delivery of commercially available dosage forms, including influenza vaccines, lidocaine, and insulin for humans [55].

The most common and less invasive methods to improve drug penetration through the skin barrier

are based on either removing the outermost layer of the skin by peeling off the tape or using various chemical enhancers such as dimethyl sulfoxide, ethylenediaminetetraacetic acid (EDTA), sodium glycocholate and related cholates, Tween 20 (non-ionic polysorbate surfactant), Brij 35 (polyoxyethylene lauryl ether), saponins, bile salts. Typically, penetration enhancers are small molecules that temporarily soften the bond between adjacent cells of the corneal epithelium (EDTA) or increase the fluidity of membranes (cholates) [55]. Oleic acid, the most studied unsaturated fatty acid, is a component of the transdermal composition Vivelle® estradiol, acting as a permeability enhancer along with propylene glycol [56] and peptides (both for macro molecules and micromolecules) [57].

A few implantable sensors for continuous monitoring of body characteristics have been developed and released [58]. The identification device RFID tag developed by VeriChip Corporation is a great example of a successful implantable device. This device optionally can be implanted in the upper arm where the medical professionals use the serial number emitted by the VeriChip in order to enable rapid obtaining of the vital data regardless of people's availability [58, 59]. Recent advances in biosensors offer novel solutions of a variety of tasks such as control over glucose level, pregnancy and DNA testing, microRNA detection, etc. [60].

Conclusion

Thus, emerging technologies in the field of novel microelectronics, sensors, miniaturization techniques, and biomaterials lead to an investigation of implantable drug delivery and monitoring systems. Problems in traditional routes of drug absorption and dosage forms stimulate the development of novel designs for drug delivery which in some cases are accompanied by the bidirectional connection. One of the most promising approaches based on transdermal delivery of carriers loaded with drugы as it helps to avoid unnecessary invasive intervention. However, transdermal delivery is limited by a number of diseases that can be treated in this way. In this paper we provided information about the most interesting and promising strategies from our point of view that optimize the drug delivery process using various compositions of nano- and microcarriers of different nature and design, special physicochemical amplifiers, various devices, and methods. We hope to encourage other researchers to go beyond the traditional methods of drug delivery and put into practice new ones.

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Стратегии в области наномедицины и доставки лекарств для применения в тераностике

А. В. Ермаков, Е. В. Ленгерт, С. Б. Вениг

Ермаков Алексей Вадимович, Саратовский национальный исследовательский государственный университет имени Н. Г. Чернышевского; Первый Московский государственный медицинский университет имени И. М. Сеченова, отдел биомедицинской инженерии, ermakov.ssu@gmail.com

Ленгерт Екатерина Владимировна, Саратовский национальный исследовательский государственный университет имени Н. Г. Чернышевского, lengertkatrin@mail.ru

Вениг Сергей Борисович, доктор физико-математических наук, профессор, Саратовский национальный исследовательский государственный университет имени Н. Г. Чернышевского, sergey.venig@gmail.com

Системы на основе подходов наномедицины и доставки лекарств являются относительно новой, но быстро развивающейся отраслью науки, которая исследует материалы в диапазоне нано- и микромасштабов в качестве инструментов диагностики или носителей для доставки терапевтических средств к определенным целевым участкам в организме. В данном обзоре кратко представлены достижения последних лет в области наномедицины и систем доставки лекарств на основе наноматериалов и носителей лекарственных средств различного состава, специфических физико-химических усилителей, различных устройств и методов. Рассматриваются и сравниваются несколько основных стратегий доставки систем для терапии и диагностики *in vivo*, включая инъекции, имплантацию и трансдермальную доставку. Все эти пути обладают определенными преимуществами относительно абсорбции лекарственных средств, доставки их к заданным участкам организма, пролонгации их действия, снижения дозировки и многих других параметров, которые необходимо учитывать для обеспечения правильного подхода к лечению конкретного заболевания. Обсуждаемые здесь инновационные подходы к доставке лекарств открывают возможности для эффективного лечения широкого спектра заболеваний, которые невозможно победить традиционными подходами, особенно хроническими. Хотя трансдермальная доставка предполагает под собой многообещающий неинвазивный способ лечения различных заболеваний, относительно хронических заболеваний имплантация устройств для доставки лекарств с двунаправленной связью является более эффективным подходом, что в будущем может значительно улучшить качество жизни. Разнообразие появляющихся технологий в микроэлектронике, сенсорах и биоматериалах приводит к кардинальным изменениям в медицинской промышленности и появлению новых систем, обеспечивающих лечение в рамках тераностики.

Ключевые слова: наномедицина, доставка лекарств, тераностика, имплантирование, трансдермальные системы.

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