https://doi.org/10.33380/2305-2066-2021-10-1-57-66
UDC 615.1

Review article / Обзорная статья

Ophthalmic Drug Delivery Systems (Review)

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Received: 26.10.2020. **Revised:** 14.12.2020. **Published:** 25.02.2021

Abstract

Introduction. Effective delivery of ophthalmic drugs is challenging. The eye has a number of protective systems and physiological barriers, which is why ophthalmic dosage forms have a low bioavailability, usually not exceeding 5 %. Topical drug administration is relatively easy to use and is most commonly prescribed by physicians for the treatment of ophthalmic diseases, especially the anterior segment of the eye. However, when using traditional delivery systems, a number of problems arise: patients' violation of the drug administration technique, and, as a consequence, a decrease in treatment compliance, restriction of drug delivery to the target eye tissues due to low epithelial permeability and rapid clearance after drug administration. Maintaining a constant therapeutic drug level is another challenge that traditional delivery systems often fail to cope with.

Text. The article discusses the types of ophthalmic delivery systems. Traditional ones are represented by such dosage forms as eye drops, ointments, gels. Modern ophthalmic dosage forms are represented by: eye films, contact lenses and eye implants. The characteristics, advantages and disadvantages of each type of delivery systems and their promising directions of development, as well as modern developments in this area are given.

Conclusion. Currently, most of the scientific research on the development of ophthalmic delivery systems is devoted to obtaining dosage forms capable of maintaining a constant concentration of the drug in the target tissue, providing the transport of active ingredients to them. This is achieved by using modern advances in nanotechnology and polymer chemistry. Receive liquid and soft dosage forms with micro-, nano- and micro-nano-carriers. Polymeric delivery systems such as films, lenses and implants are being actively developed and studied. The development of modern technological approaches opens up new possibilities for the treatment of a wide range of ophthalmic diseases by reducing the side effects often induced by the intrinsic toxicity of molecules, reducing the frequency of the administered dose and maintaining the pharmacological profile of the drug. Thus, the use of modern ophthalmic delivery systems can significantly limit the use of invasive treatments.

Keywords: ophthalmic delivery systems, ophthalmic dosage forms, drops, gels, nanosystems, ocularinserts, ophthalmic implants, packaging.

Conflict of interest: no conflict of interest.

Contribution of the authors. Elena O. Bakhrushina, Maria N. Anurova, Natalia B. Demina, Ivan I. Krasnyuk developed the concept and research methodology. Elena O. Bakhrushina, Ivan V. Lapik, Anastasia R. Turaeva were engaged in the collection and analysis of literature data. Elena O. Bakhrushina, Maria N. Anurova, Natalia B. Demina participated in writing the text of the article. Elena O. Bakhrushina, Maria N. Anurova, Ivan V. Lapik were engaged in data processing. Ivan I. Krasnyuk supervised the work. All authors participated in the discussion of the results.

For citation: Bakhrushina E. O., Anurova M. N., Demina N. B., Lapik I. V., Turaeva A. R., Krasnuk I. I. Ophthalmic drug delivery systems. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2021;10(1):57–66. (In Russ.). https://doi.org/10.33380/2305-2066-2021-10-1-57-66

Системы доставки офтальмологических препаратов (обзор)

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Статья поступила: 26.10.2020. **Статья принята в печать:** 14.12.2020. **Статья опубликована:** 25.02.2021

Резюме

Введение. Эффективная доставка офтальмологических лекарственных препаратов является сложной задачей. Глаз имеет целый ряд защитных систем и физиологических барьеров, из-за чего офтальмологические ЛФ имеют низкую биодоступность, обычно не превышающую 5 %. Местное применение лекарственных препаратов – относительно простое для использования и наиболее часто назначаемое врачами для лечения офтальмологических заболеваний, особенно переднего сегмента глаза. Однако при использовании традиционных систем доставки возникает ряд проблем: нарушение пациентами техники введения лекарственных средств и, как следствие, снижение комплаентности лечения, ограничение доставки лекарственных препаратов к целевым тканям глаза из-за низкой проницаемости эпителия и быстрого клиренса после введения препарата. Поддержание постоянного терапевтического уровня препарата еще одна проблема, с которой традиционные системы доставки зачастую не справляются.

Текст. В статье рассмотрены виды офтальмологических систем доставки. Традиционные представлены такими лекарственными формами, как глазные капли, мази, гели. Современные офтальмологические лекарственные формы представлены глазными пленками, контактными линзами и глазными имплантатами. Приведены характеристика, достоинства и недостатки каждого вида систем доставки и их перспективные направления развития, а также современные разработки в этой области.

Заключение. В настоящее время большая часть научных исследований по разработке офтальмологических систем доставки посвящена получению лекарственных форм, способных поддерживать постоянную концентрацию АФИ в ткани-мишени, обеспечивающих транспорт действующих компонентов к ним. Это достигается использованием современных достижений в области нанотехнологий и химии полимеров. Получают жидкие и мягкие лекарственные формы с микро-, нано- и микро-нано-носителями. Активно разрабатываются и изучаются полимерные системы доставки, такие как пленки, линзы и имплантаты. Развитие современных технологических подходов открывает новые возможности для терапии широкого круга офтальмологических заболеваний за счет снижения побочных эффектов, часто индуцируемых собственной токсичностью молекул, снижения частоты вводимой дозы и поддержания фармакологического профиля лекарственного препарата. Таким образом, использование современных офтальмологических систем доставки способно существенно ограничить применение инвазивных методов лечения.

Ключевые слова: офтальмологические системы доставки, глазные лекарственные формы, капли, гели, наносистемы, глазные пленки, глазные имплантаты, упаковка.

Конфликт интересов: конфликта интересов нет.

Вклад авторов. Е. О. Бахрушина, М. Н. Анурова, Н. Б. Демина, И. И. Краснюк разработали концепцию и методологию исследования. Е. О. Бахрушина, И. В. Лапик, А. Р. Тураева занимались сбором и анализом литературных данных. Е. О. Бахрушина, М. Н. Анурова, Н. Б. Демина участвовали в написании текста статьи. Е. О. Бахрушина, М. Н. Анурова, И. В. Лапик занимались обработкой данных. И. И. Краснюк руководил работой. Все авторы участвовали в обсуждении результатов.

Для цитирования: Бахрушина Е. О., Анурова М. Н., Демина Н. Б., Лапик И. В., Тураева А. Р., Краснюк И. И. Системы доставки офтальмологических препаратов. *Разработка и регистрация лекарственных средств*. 2021;10(1):57–66. https://doi.org/10.33380/2305-2066-2021-10-1-57-66

INTRODUCTION

In modern ophthalmology, *compliance* of patients with such chronic diseases as glaucoma, cataract, age-related macular degeneration, dry eye syndrome is especially challenging. According to the published data, the main problems preventing high patients' treatment compliance is untimely specialist's referral, not a regular administration of the prescribed drug, as well as, problems with correct *instillation* [1, 2].

Thus, to increase patients' compliance to eye disease therapy, advances in development of new ophthalmic dosage forms and modern package become essential [1–4].

HISTORY

The local drug administration through eyes via instillation to the conjunctival sac has been practiced since ancient times. The formulations of ophthalmic dosage forms were found on Egyptian papyruses, and since 20 years BC to 50 years AD, Greek and Roma people practiced delivery of necessary components of eye dosage forms diluting them in water, milk and egg white. Term "collyrium" was used for the resulting liquid dosage form [5]. In the Middle Ages, collyria were used for cosmetic purposes: they were used for atropine instillation to dilate pupils. Subsequently, Rome collyria gave birth to modern dosage form "eye drops" [6]. Up to 40-s of the XX century, ophthalmic products were manufactured exclusively in the settings of pharmacy production and were intended for the use immediately after production [6]. In 1953, the FDA adopted the provision according to which all non-sterile ophthalmic products were considered as falsified, and in 1955, the sterility requirement was included to the American Pharmacopeia [7]. The first ophthalmic product in the dosage form other than the true solution was developed and further commercialized in 1950-s. Cortisone acetate suspension became such drug which led to the expansion of variety of the dosage form group [8].

The next stage was the discovery of efficacy and prolonged effect of eye gels thymol maleate based on gellan and xanthan gums in 1982 by Japanese investigators S. Hosaka et al [9]. In the beginning and mid 90-s of the XX century, the role of gelation agents in the

modified release of active pharmaceutical ingredients (API) and increase of patients' compliance to treatment with such products was proven [10]. The introduction of polymers to ophthalmic products allowed to increase time of API contact to corneal surface which increased its bioavailability. In 1997, K. J. Sullivan et al. first mentioned the positive role of gelation agent carbomer in elimination of dry eye syndrome [11].

MODERN DEVELOPMENT VECTORS OF OPHTHALMIC DOSAGE FORMS

Despite a wide variety of ophthalmic dosage forms, modern investigators are to overcome low bioavailability of ophthalmic drug products (DP) which amounts to 0.5 to 5 % [12]. It is due to short contact of a dosage form with eye conjunctiva in instillation, the complex anatomic eye structure, low absorbing surface and corneal lypophylicity, metabolism, fermentation, API binding with proteins contained in the lacrimal fluid, as well as protective mechanisms: tear formation of tears, blinking and substance flow through the nasopharyngeal passage [13]. Low capacity of a conjunctival bag (about 30 µl without blinking), absorption from the palpebral conjunctiva (lining up internal eyelid and protective mechanisms cause the decrease in API concentration of AFI and reduce retention time of an ingredient in the absorption site [14]. The bioavailability of ophthalmic products is also affected by pH, chemical structure of API, DP, solvent used, osmolality, drug viscosity [1, 12].

The ophthalmic drug delivery systems of delivery contact with lacrimal liquid and eye surface tissue. Lacrimal liquid (7 µl) forms the thin layer consisting of three parts: an outer lipid layer (200 Nm), aquatic layer (3–7 µm) containing mucins and other soluble proteins and a mucin-containing gel layer (1 µm). Low molecular compounds penetrate through the cornea and a conjunctiva by passive diffusion (transcellular and/or paracellular). Compounds with molecular weight up to 5 kDa may penetrate into the conjunctiva while the sclera may passes macromolecules with a molecular weight up to 100 kDa [12].

VARIETY OF OPHTHALMIC PRODUCTS

Ophthalmic products for local application can be applied to eyelid skin, injections to the conjunctival sag, to eye tissues (anterior and posterior chambers, the vitreous body) and surrounding tissues. According to general pharmacopeial monograph "Eye Dosage Forms", *liquid* ophthalmic dosage forms include: eye drops representing solutions/suspensions/emulsions, eye instillation solutions (eye lotions), subconjunctival, parabulbar and intraocular solutions; soft DF: eye ointments, eye gels, eye creams; *solid* DF: powders and tablets for eye solutions, eye films, eye implants.

Nowadays over 350 ophthalmic drug products are registered in the Russian Federation. 89 % of drugs are represented by eye drops, 10% are soft DF, among them, 19 % are eye gels.

New forms of delivery systems which have been recently investigated include microemulsions, nanoparticle solutions, multicomponent carrier systems, eye films, lenses, collagen screens and also so-called gels *in situ* are polymer solutions which turn to gels on the mucosa [3, 4, 13, 14]. On the US and European pharmaceutical market, there are also drug compositions as ophthalmic microtablets to be administered behind the eyelid and ophthalmic sprays [15–17].

EYE DROPS

Eye drops are the oldest and most widely used ophthalmic dosage form. When eye drops are instilled, a dosage form is rapidly absorbed from the conjunctiva, and the absorption depends on its solubility, concentration (highly concentrated solutions are absorbed more rapidly) and pH. The main disadvantages of eye drops are short-term mucosal effect, DF evacuation from the mucosa and large drug consumption.

One of prospective methods of the increase in API bioavailability in eye drops is introduction of specific penetrating agents, for example cyclodextrins, crown ethers, chelating agents, surfactants, etc. to their structure [18].

Cyclodextrins – cyclic oligosaccharides forming complex compounds with API thereby increasing their solubility and not changing molecular structure. Cyclodextrins allow to retain hydrophobic drug substances in a solution and to transfer them to the surface of biomembranes [18, 19]. In ophthalmic products, the optimum API bioavailability is reached with concentration of cyclodextrins (<15 %) in a solution. 2-hydroxypropyl-β-cyclodextrins is one of the most of-

ten used cyclodextrins which does not a have an irritant action. The eye drops containing complexes of dexamethasone and pilocarpine with 2-hydroxypropyl-β-cyclodextrin are developed and commercialized – these products are well-tolerated and provide a higher bioavailability compared to common eye drops [18–21].

Crown ethers represent the synthetic cyclic oligomers of ethylene oxide consisting of bound ether radio groups. Crown ethers are called so owing to the typical molecule form. These compounds may form complexes with metal ion metals and with neutral and ionic organic molecules, and their complexes may penetrate through biological membranes. Amphiphilicity of crown ether molecules makes them ideal candidates to be introduced into ophthalmic delivery systems of as permeability enhancers. In their work, Morrison et al [22] investigated the possibility to use crown ethers 12C4, 15C5 and 18C6 for use in ophthalmic riboflavin delivery systems therefore API solubility increased in an aqueous solution up to 46 % in vitro potentially increasing riboflavin penetration into cattle cornea [18, 22].

Microemulsions belong to potentially perspective carriers for eye drops. Microemulsions are relatively simple to produce, can be sterilized, are kinetic stable colloidal systems. They are widely used as delivery systems owing to their ability to dissolve both lipophilic, and hydrophilic drug substances and also to increase API bioavailability For production of microemulsions such non-ionic surfactants as tweens and span (tween-80 and span-60) are used, which are hypoallergenic and non-toxic surfactants allowed for the use in ophthalmology. The clinical trials have shown efficacy and high bioavailability of drugs used as ophthalmic microemulsions. API for which microemulsion eye drops were developed, – antibiotics chloramphenicol, moxifloxacin, cyclosporine A and also flurbiprofen [23–25].

To increase API bioavailability and its protection from enzymes of the corneal epithelium, liposomes are also used. Liposomes are spherical compounds which are formed in API and phospnuholipid solutions which usually consist for example, of phosphatidylcholine, stearylamine and various concentrations of cholesterol or lecithin, and α-L-dipalmitoyl phosphatidylcholine. Liposome advantages contain: biocompatibility, biodegradability, amphiphilic properties and low toxicity. The efficiency of API delivery from liposomes depends on numerous factors, namely: encapsulation efficiency, the size and a charge of liposomes, stability of liposomes in a conjunctival sag and affinity to the corneal surface. The liposomes loaded positively compared with liposomes loaded negatively and neutrally show higher affinity to the negatively charged surface of the cornea and conjunctival mucoglycoproteins, due to that, slow down API elimination from application area. To increase adhesion of negatively and neutrally loaded liposomes to the corneal or conjunctival surface, liposome suspensions may be introduced to mucoadhesive gels or their combinations with mucoadhesive polymers. Nowadays, liposome-based ophthalmic agents are developed for such API as acyclovir, pilocarpine, acetazolamide, chloramphenicol and ciprofloxacin [25–29].

SOFT OPHTHALMIC DFs

Soft ophthalmic DFs are intended for conjunctival (ointments and creams) and eyelid, and corneal applications (gels). Soft DFs are used in ophthalmologic practice for ensuring local action – DFs are demanded for antibiotics and hormonal agents, antiviral, antifungal products, regenerative agents, etc. Disadvantages of the dosage forms may include a temporary decrease in visual acuity after their application.

The most perspective ophthalmic soft DF are gels. Inconvenient dosing may be their disadvantage [1]. The application of gels *in situ* allows to combine convenience of use and new technologies of liquid DF delivery with the advantages typical for soft DFs [3]. Gels *in situ* are viscous fluids which may perform sol-gel-transition being influenced by external factors, such as corresponding pH, temperature and presence of electrolytes. The DF is available in all possible variants of liquid DF packages that will provide dosing accuracy and convenience of instillation. Being applied to the cornea, a DF changes its rheological characteristics, from liquid into viscoplastic condition. This feature leads to the delayed drainage of drugs from the corneal surface and to the increase in API bioavailability. Polymers which can provide medium-dependent sol-gel-transition on the eye mucosa are poloxamers, gellan and xanthane gum, alginic acid salts, cellulose acetate phthalate. Compositions of gels in situ

are developed for production of drugs ciprofloxacin hydrochloride, maleate timolol, fluconazole, acyclovir and pilocarpine [30–32].

Gellan gum has high potential as an excipient for ophthalmic delivery systems combined with other polymers owing to the increased drug exposure time on the mucosa and a proven greater API bioavailability [33]. Chemical modification of gellan gum (for example, methacrylation) leads to enhancing of API therapeutic effect in the delivery system as it is shown by L. E. Agibayeva et al. [34] in the study in vivo of delivery systems of pilocarpine hydrochloride containing gellan gum and its methacrylated derivatives.

Another prospective direction for development of eye gels is the introduction of micro, nano- or micro-nano-carriers to the composition. Owing to the combination, it is possible to achieve the prolonged and controlled release, increase in bioavailability and to protect API from the enzymatic metabolism present on the eye mucosa. Using positively charged bioadhesive polymers, it is possible to achieve the enhanced interaction with negative charges on the corneal surface and the increased time of pre-corneal retention and drug absorption [35–37]. For example, it is shown that the nanoparticles introduced to gels produced from chitosan or poly-ε-caprolactone showed the 25-fold increase in celecoxib bioavailability compared to celecoxib suspension in rats. Moreover, celecoxib concentration was increased both in anterior and posterior eye segments [37]. Carbomer 934 hydrogel with proprofen nanoparticles from poly lactic glycolide polyether has shown the significant increase in corneal permeability and lower irritant action in comparison with commercial proprofen drops [36].

EYE FILMS

Eye films (*ocular inserts*) – the term generally accepted by modern pharmacopeias consolidating the wide range of the solid DFs to be administered within the conjunctiva. In particular, eye lenses, collagen screens, eye therapeutic systems belong to eye films [14].

As dosage forms, the films have been known from 60-s of the 20th century [38]. In the USSR, the employees of the All-Union Scientific Research Institute of Medical Equipment together with the staff of the Helmholtz Moscow Research Institute of Eye Diseases invented and successfully approved eye medical films with sulphapiridazine, neomycin sulphate, kanamycin and other API. The films with pilocarpine registered in the USSR in 1980 had a prolonged anti-hypertensive action, were well-tolerated by patients as they were small-sized and superior to eye drops of pilocarpine [39].

Eye films are less susceptible to physiological protective mechanisms of an eye, such as outflow through the nasopharyngeal cannel, may remain within the conjunctival sac for a longer period compared to conventional liquid and soft eye dosage forms, are more stable. Their definite advantages are dosing frequency, the possibility of a prolonged API release and minimization of systemic effect and, as a result, a systemic adverse effect. Moreover, their use allows to reduce dosing frequency and blurred vision typical for soft ophthalmic dosage forms. API is released from eye films owing to uniform diffusion from a film to lachrymal fluid with a constant rate during the assigned period. Disadvantages of eye films may include a sensation of a foreign body in the eye in their application, difficulties of DF application, the possibility of imperceptible film removal from the eye. Application of eye films requires special instructing and training of patients [14, 38].

The studies of the leading companies (Alcon, Bausch & Lomb Incorporated, Johnson & Johnson) specializing in ophthalmic products are focused on the development of delivery systems as eye films The modern commercialized developments are presented by collagen screens (or solution collasome), eye films based on cellulose derivatives for treatment of the dry eye syndrome, eye therapeutic systems or eye lenses [14]. Eye film Lacrisert® consists of a matrix based on hydroxypropyl cellulose. After introduction to the conjunctival sac, the film absorbs moisture from the conjunctiva and a cornea forming a hydrophilic layer which stabilizes and thickens a lacrimal film and humidifying the cornea. The product effect of medicine lasts up to 24 hours, and a special blister packing allows to produce a sterile film without addition of preservatives [40].

Collagen screens are developed from pork sclera which collagen is highly similar to human cornea. Collagen screens are kept in vacuum packing and hydrated prior to introduction to the conjunctiva. Collagen screens may be carriers of antibiotics (gentamycin), anti-inflammatory drugs (dexamethasone) or antiviral

agents. Based on the study results in vivo and clinical trials compared to eye drops, the use of collagen screens has allowed to get higher DS concentration in the cornea [13].

Recently, *contact lenses* have been more and more developed as drug delivery systems [41–43]. In the study, S. Gause et al. [41], using the mathematical modeling, showed the appropriateness of contact lenses with API and the increase in bioavailability by 50 % compared to instillation of eye drops. Contact lenses with timolol, dorzsolamide and vitamin E both alone and in combination were developed [44]. In the work by D.K. Naplekov et al. [45], the production algorithms of API solutions for loading of contact lenses and their use as delivery systems on the example of sodium hyaluronate solution were considered.

EYE IMPLANTS

Implants represent a sterile LF consisting of a polymeric matrix with API homogeneously distributed within which is released in the implantation site during the assigned period. There are biodegradable and non-biodegradable implants. The duration of API release from the biodegradable implants varies from 35 days to 12 months. The material for production of biodegradable implants is often represented by aliphatic polyethers of polyglycolic and polylactic acids and their co-polymers [46]. Non-biodegradable implants are removed after API release for prevention of their fibrosis and encapsulation in the eye cavity. As a matrix basis for such implants, polyvinyl alcohol, ethylene vinyl acetate, polybutyl methacrylate, silicone, etc. are often used [46]. Implants are produced with the method of melt extrusion or direct pressing in matrixes of various form. As a rule, eye implants are lay down with covering from the polymeric basis regulating API release [46]. At the MacClay research center in Belfast (Great Britain), ocular intravitreal implant OcuLief™ was developed [42, 43] that represents the matrix in situ, which is cross-linked after introduction of liquid drug to the posterior eye chamber under the exposure to the targeted UV-radiation.

OcuLief™ is intended for treatment of diabetic retinopathy, age-related macular degeneration and diabetic macular edema by a long release of anti-vascular endothelial growth factors or corticosteroids within 4–6 or more months [47].

PACKAGE TYPES OF OPHTHALMIC DOSAGE FORMS

Due to high prevalence of eye diseases, wide use of ophthalmic dosage forms and a challenging problem of the decrease in microbial contamination, dosing accuracy and decrease in error percentage in instillation, the development of innovative package types of ophthalmic dosage forms is especially relevant.

For packing eye drops, bottle droppers from glass or polymeric materials are traditionally used. A glass bottle fitted with a glass pipette dispenser which was widely used as pharmaceutical package for drops in the end of the XX century, is practically not used nowadays due to the proven high degree of secondary contamination through a tip of the glass dispenser. Despite the advantages of glass packing, self-cost of a glass bottle dispenser is significantly higher than the one of a similar plastic packaging produced with the resource-sparing BFS technology (Blow – Fill – Seal). Multidose glass and polymeric bottles for eye drops can have a various volume, design and construction of a dropper, the first opening control, however, a significant disadvantage of such package is a loss of product sterility after the opening and its secondary contamination. Multidose droppers may not always provide a patient's dosing accuracy. A small storage period after being opened, as well as numerous mistakes at instillation often lead to incomplete use of dosage forms in multi-dose bottles and disposal by a patient.

The problem of drug sterility loss may be solved by the use of one-dose packing produced from polymeric materials with the BFS technology. However, one-dose packing of eye drops does not solve fully the problem of dosing accuracy as it is impossible to recover 100 % of products from a one-dose dispenser. The producer should overfill a package that leads to the increase of self-cost of a product unit. Moreover, compared to a multidose bottle dispenser, one-dose dispensers in packing take a much bigger volume and are less convenient for storage and transportation.

Powders for preparation of eye drops, as well as other sterile solid dosage forms, are packed into the glass bottles sealed with rubber stoppers – and crimped aluminum cap. Powders are used in the event of pharmaceutical incompatibility of components or poor stability of a solution when stored.

Figure 1. **Principle of operation and examples of multi-dose vials using sterilizing filtration [48–49]**

Figure 2. **Innovative control systems for dosing eye drops:**
1 – AcuStream® system (Kedalion, USA); 2 – multi-dose ophthalmic system (Aerpump, Germany); 3 – multi-dose system controlled from a smartphone e-Novelia® (Nemera, France) [50–51]

Eye films are packed into a blister, a dosage form within in a package, depending on biodegradability, is under a vacuum or in isotonic solution. To reduce a risk of microbial contamination when eye film is introduced, an applicator is attached to the primary packaging.

Tubes for soft ophthalmic dosage forms, as a rule, have an extended nozzle allowing to administer a drug into the conjunctiva or conjunctival sac with the contactless method. However the percentage of secondary contamination when using soft DFs is estimated as high.

Obvious disadvantages of one-dose packing have resulted in the need of modification of traditional multidose bottle dispensers and product protection against secondary microbial contamination. Polymeric bottle dispensers fitted with a valve controlling the lack of the reverse fluid intake, a nozzle with antibacterial elements (silver ion treatment is more often used) and the built-in sterilizing air filter were developed (figure 1). When polymeric bottle is squeezed under internal air pressure, the valve is opened, a DF dose as a drop passes through a nozzle with an antibacterial covering and is gathered on a tip. After the compression, the air passes through the sterilizing filter and fills the pressure differential outside and within the packing. Nowadays, polymeric bottle dispensers of such kind are produced by many companies including Aptarpharma (Switzerland), Nemera (France), etc. [43, 44]. Instillation correctness minimizing or excluding dose loss, as well as, dosing accuracy compliance are controlled with the innovative delivery systems of liquid ophthalmic DFs (figure 2). So, AcuStream® system works using the special device spraying out liquid DF on the eyeball mucosa. The orientation of a dispersion torch, dispersion of a drop phase and dosing accuracy provide high DF bioavailability [50].

Company Nemera has offered system Novelia®, system including a polymeric bottle dispenser Novelia® fitted with the valve protecting against secondary contamination. Owing to the applicator nozzle corresponding to the anatomic structure of an eye-socket, the percentage of wrong instillations is minimized, and dose volume and necessary pressure at the injector is provided automatically and is controlled by the smartphone program [51].

The search of optimal solutions for introduction of liquid ophthalmic dosage forms ensuring their quality throughout the expiry period continues and is still a challenging task.

CONCLUSION

Nowadays, the most scientific research on development of ophthalmic delivery systems is devoted to production of DFs which may maintain constant API concentration in a target tissue providing API transport to them. It is achieved with the use of modern achievements in nanotechnologies and polymer chemistry. Liquid and soft dosage forms are produced with liposomes and nanoparticles as delivery systems, introducing various penetrators to the structure. Polymeric carriers such as films, lenses and implants are actively developed and investigated. The development of modern technological approaches opens new opportunities for therapy of a wide range of ophthalmic diseases due to the decrease in adverse effects which are often induced by inherent toxicity of drug product molecules, the decrease in dosing frequency and maintenance of drug pharmacological profile. Thus, the use of modern ophthalmic delivery systems can significantly limit invasive treatment methods.

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