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Review Article

OCULAR INSERETS AS A MODERN THERAPY TREND IN OPTHALMOPATHOLOGY

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ABSTRACT

Ocular insert (OI) has its wide recognition and importance from the 19th century around the world, the use of this dosage form in clinical practice was distributed throughout the USSR. The key issue covered in this review is the development of the ocular insert and their testing by specific parameters of quality. It is important to choose the right excipients and standardize ocular inserts according to pharmacopoeia articles (thickness, pH, biodegradation time). It is also important to control those indicators that increase patient compliance. Technology of solid dosage form consists of several stages: mixing, drying and cutting with packaging in primary polymer packaging. So the manufacturer does not need highly specialized equipment and staff skills. Based on this information, we can concluded that ocular inserts are promising and actively researched dosage form, which in the future, could fully complement or replace the medical drugs traditionally used in ophthalmology.

Keywords: Ocular insert, Polymers, Quality tests, Dosage form development, Ocular insert manufacturing

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INTRODUCTION

At this moment, the creation of ophthalmic drug delivery system is an actual and challenging task, which is facing scientists all over the world. The main problem associated with the ophthalmic drugs using is the inability of the drug to maintain the necessary local therapeutic effect for a long time. Traditional dosage forms, such as eye drops, ointments or gels, do not provide the required maintenance content duration of active pharmaceutical ingredient (API) and bioavailability of the drug, which is 1-10% for local ophthalmic drugs. Low bioavailability may be associated with the protective mechanisms of the eye, complex anatomical structure, small adsorption surface, lipophilicity of the corneal surface or, interaction with tear proteins, etc. The small volume of the conjunctival sac and the above factors reduce the concentration of the drug and shorten the time that the drug is at the site of introduction [1-3]. Also, the concentration of the API often dependent on the correctness of the patient's installation of the drug and adhering to the dosage regimen. The low bioavailability of eye drops leads to an increase in the frequency of instillation to achieve the required API content on the ocular mucosa, which provokes the development of systemic side effects. The problem of low efficacy of traditional liquid and soft dosage forms can be solved by the development of a solid dosage form–the ocular insert (OI), which helps to prolong the release of API. Such ocular inserts have appropriate quality parameters and a relatively simple manufacturing technology, unlike other solid dosage forms used in ophthalmology, such as implants.

The review was created using databases as PubMed, Google Scholar, Elibrary, Clinical Trials with the following terms "ocular inserts", “ocular film”, "inserts", "ocular insert development", "ocular insert drying", "ocular insert technology", "ocular insert manufacturing" and "ocular insert packaging" in period from 1950 to 2023 to fulfill all retrospectives of OI.

Ocular insert characteristics

Today, OI is one of the most promising ophthalmic dosage forms. Foreign literature, according to PubMed. com to denote OI, both term "insert" (49/61, where 61 is the number of articles analysed) and «film» (12/61). However, in the registries of countries, the registration of medicines in the form of the ocular insert is designated only as "insert". Combining pharmacopoeial terms, an OI- is a solid dosage sterile ocular insert dosage form intended for placement in the conjunctival sac containing one or more API.

Externally the OI is a rigid elastic plate of oval or rounded shape with a size of 6x9 mm, a thickness of 0.35 mm and a weight of 0.015 g. Desorption of the API from the ocular insert occurs by three main mechanisms: diffusion, osmosis or bioerosion [1, 4].

With this diffusion, the drug is continuously release date a controlled rate through the polymer membrane (semi-permeable or microporous) into the tear fluid. After placing the OI on the surface of the eyeball, water from the tear fluid begins to penetrate into the matrix, after which it to swell, relaxing the polymer chain with further diffusion of the active substance (fig. 1A). If the OI is made of an insoluble (non-erodible) material, the release of the API will occur by diffusion through the pores (fig. 1B).

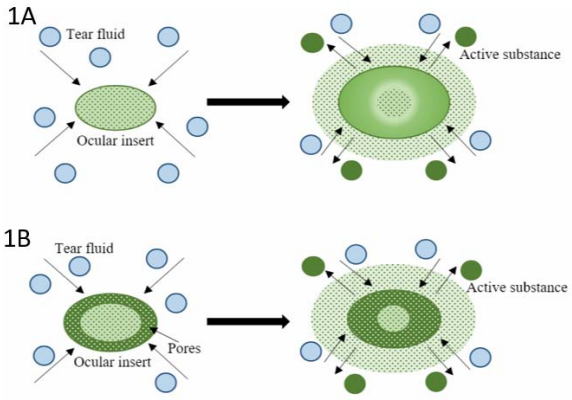

Fig. 1: Release of active substances by diffusion mechanism: 1A- Swelling of the ocular insert with the release of API; 1B-API release through a microporous membrane

In the case of bioerosion, the OI should consist of a biodegradable matrix into which the drug is directly evenly dispersed. So, when the OI comes into contact with the tear fluid, there is a controlled release of API with simultaneous destruction of the matrix (fig. 2).

The osmosis mechanism is designed so that when the OI meets the cornea the tear fluid diffuses through a semi-permeable membrane into a chamber with an osmotic substance, which leads to its stretching and at the same time, compresses the reservoir containing the active ingredient. As a result, the drug is released through a special hole (fig. 3).

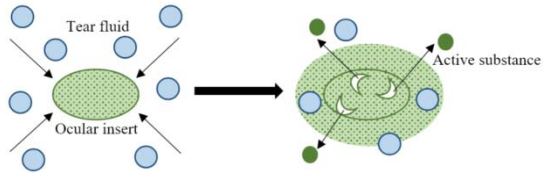

Fig. 2: Release of active substances by bioerosion mechanism

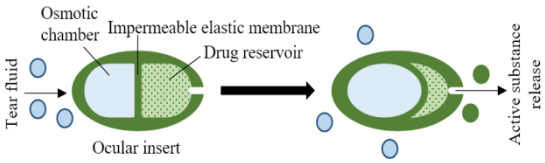

Fig. 3: Release of active substances by osmosis mechanism

The prospects for the use of OI are because, unlike the soft and solid dosage forms traditionally used in ophthalmology, they are less susceptible to the protective eye barriers, such as tear production in the conjunctival cavity followed by nasolacrimal drainage, corneal permeability, conjunctival blood flow and others [5]. This feature ensures the stability of the OI provided a prolonged therapeutic effect with controlled release of the required API amount in a given period, avoiding the phenomenon of dose loss inherent in the installation method. There is also a high probability of infection of the second eye with liquid and soft dosage forms, the reason for which is non-compliance with the drug regimen when, after installation in an infected eye, the patient does not properly wash his hands and continues to manipulate the second eye, in which there is no reproduction of bacteria. Thus, the use of OI in ophthalmic practice makes it possible to achieve accurate drug dosing, maintain the required API concentration, reduce the frequency of its administration and thereby minimize the development of a systemic side effect and the risk of cross-contamination [6].

In addition to the advantages of OI, the solid dosage form has significant disadvantages–strict adherence to drug administration rules. Both before using the ocular insert and eye drops and ointments, the patient should wash his hands with soap or treat them with an antiseptic. Then remove the tweezers (contents of the primary package) and rinse it under running water to strengthen the adhesion of the medicinal drug to the auxiliary construction; remove the OI and place it on the lower eyelid after gripping it with the free hand [7]. To reduce the likelihood of eye injury, it is recommended that manipulations are performed at a calm pace in front of a mirror. An undoubted advantage is the fact that the biodegradable OI does not need to be removed from the eyelid and the patient, thanks to the prolonged action of the form, is exempt from further therapy during the day.

Patients with comorbidities associated with hand tremor are unable to place the OI on the lower eyelid due to the high injury risk of tweezers, so their use is limited to the presence of another person nearby. Using OI is also difficult to people with pokaphobia (fear of touching the cornea of the eye).

Despite the patient's aspect OI has more manufacturing stages then eye drops, the drying is an additional process between stirring and packaging. The moisture loss should be developed in accordance with API nature (e. g. thermolability) and cost-effectiveness of manufacture. Special drying conditions as temperature, vacuum, air circulation play a great role in OI development due to this fact scale production is quite unpredictable [8].

Contrary to the limitations in potentially possible patients using OI, the dosage form ensures the pharmacological efficacy of the drug and minimizes the risk of side effects due to the absence of secondary cross-contamination.

Retrospective of OI in the world

The precursor to OI is the medicinal form of lamellae, which are small oval gelatin discs 3 mm in diameter containing various API in the composition base. Until the middle of the 20th century, lamellae were an official medicinal form and were presented in the pharmacopoeias of various countries; however, the lamellae use came to an end when sterility requirements for ophthalmic drugs became more stringent [9]. The preparation of this dosage form requires certain aseptic conditions; moreover, the use of gelatin mass does not guarantee the stability of the drug, which results in a reduction in shelf life. In addition to the difficulties of industrial production of the drug, the use of lamellae was limited by excessive swelling of the gelatin mass on the mucous membrane of the eye and the development of cross-contamination and aggravation of infection [10].

In the 1970s, the American company Alza announced the first ophthalmic controlled delivery system for glaucoma treatment. The drug Ocusert® was an insoluble ocular insert that was injected into the conjunctiva sac and used for controlled delivery of pilocarpine for 7 d. Compared to the traditional instillation method of treatment, Ocusert® had a number of advantages, such as a reduction in the frequency of drug application, controlled release of the active substance, less effect on accommodation and myosis, etc. However, the use of the OI was also associated with side effects such as foreign body sensation and pain in the eye, blurred vision, and difficulty holding the OI in the lower eyelid. As a result, low patient compliance led to the withdrawal of Ocusert® from the pharmaceutical market [10, 11].

To date, only 4 names of drugs related to OI have been registered in some countries of the global pharmaceutical market (table 1).

Table 1: Worldwide registered OI

Country	OI	Manufacturing authorization holder
Russia [12]	• Taurin®	• LLC NCK-Progress, Russia
USA [13]	• Dextenza®; • Lacrisert®	• Ocular Therapeutix, USA; • Bausch and Lomb, USA
France [14]	• Mydriasert®	• Laboratoires Théa, France
Spain [15]	• Mydriasert®	• Laboratoires Théa, France
Sweden [16]	• Mydriasert®	• Laboratoires Théa, France
Finland [17]	• Mydriasert®	• Laboratoires Théa, France

The most widely used OI in the world is Mydriasert® (Laboratoires Théa, France), which contains two APIs, tropicamide and phenylephrine. It is used to maintain mydriasis (dilation of the pupil) before surgery or for diagnostic purposes [18].

Lacrisert® (Bausch and Lomb, USA) is a matrix based on hydroxypropyl cellulose and used for the treatment of dry eye syndrome. Once inserted into the conjunctival sac, it absorbs moisture from the conjunctiva and cornea, thereby creating a hydrophilic layer that stabilizes the tear film and moisturizes the cornea [19].

Dextenza® (Ocular Therapeutix, USA) is an intracanalicular OI inserted into the lacrimal channel through the lower nasolacrimal duct. It is designed to deliver a reduced dose of corticosteroid (dexamethasone) to the ocular surface for up to 30 d. After

treatment, the insert dissolves and exits the nasolacrimal system without the need for removal. The field of application of intravascular insertion is used to treat ocular inflammation and pain associated with the postoperative period [20].

Of particular interest is the fact that OI is not present in all markets–for example, in drugs in this dosage form are registered in the Asian market (Malaysia, Japan, China). In addition, Mydriasert® is registered in most of the registries reviewed where OI is present providing more opportunity for competition from other companies actively developing ophthalmic medical drugs.

Clinical trials of OI

Clinical trials conducted in order to obtain data on its effectiveness and safety are an integral part of the life cycle of the medicinal drug. For OI this stage is particularly important, which allows not only to establish a guarantee of patient's health protection but also to show high therapeutic and preventive effectiveness of the new medicinal drug compared to the traditionally used treatment methods.

To assess the effectiveness of OI use in preoperative therapy and diagnostic surveys in 2004, the hospital Center of the University of Bodro in France was conducted a study of the drug Mydriacert® (Thea Laboratories, France) on the traditional method of treatment of eye drops in preparation for fluorescent angiography. The total number of patients involved in the trial were 72 people whose age varied within 64.0±16.3 y. According to the results obtained the average diameter of the pupil in both groups was the same (mydriasert® group: Ø = 7.4±0.5 mm; control group: Ø = 7.4±0.4 mm). The time of achieving sustainable midriasis in Mydriactert ® group was longer for 10 min, but the recovery of near vision an average was shorter for 15 min compared to standard treatment. When determining the API quantity required to fix the stable diameter of the pupil (~7.0 mm), it was found that the concentration of tropicamide and phenylephrine in the control group is 5-10 times higher than the same value in OI group [21].

Also known OI studies on babies that demonstrate the possibility of insert application not only in pediatric practice, but also in non-orthodox. In France from 2006 to 2008, the Mydriactert® study was conducted based on the non-anthological Robert Derby's hospital, whose purpose was to determine the average efficiency and safety of OI compared to the installation of eye drops of vaseloscopic study. According to the results, during 75 min, midriasis successfully reached 97.5% in alternative OI group patients compared to 90% of the children receiving standard eye drops treatment. The pupil diameter remained stable in 60.0% of patients with OI therapy while the installation was only 15% [22].

To assess the effectiveness of the OI use in antibacterial therapy in patients suffering from cataract, between 2008 and 2010 in Ufa Research Institute of eye diseases (Russia) there was conducted a clinical levofloxacin insert testing. Forty participants (40 eyes) of the control group in turn, also underwent antibacterial therapy 0.5% solution of levofloxacin before the cataract removal operation. According to the obtained data, the OI had a good patient tolerance, there was no sense of burning, and no signs of allergic reactions, irritation and side effects were revealed. It was also found that in the levofloxacin OI application content of API in water-water moisture of the eyeball was 6.45±0.05 μg/ml, which is 5 times higher than when installing this active substance (1.3±0.01 μg/ml). In comparison of the duration of treatment, it was noted that the average period of stay in hospital in the study group was not more than 2 d, while in the control–from 4 to 8 d [23].

To assess the OI effectiveness and safety for pain and inflammation prevention in the postoperative period clinical trials of the Dextenza® was conducted, which medical drug is an intrakalicular OI for slow introduction of a reduced dexamethasone dose on the ocular surface for 30 d. All study participants (30 people), had a planned non-laid bilateral cataract removing operations. Patients 'eyes were conditionally divided into control group receiving standard treatment with 1 % eye drops of prednisolone acetate, and experimental steroids delivery as was using of Dextenza® before operation. In assessing pain sensations statistically significant differences between the control and the main group were not identified. According to the survey, 29 participants of the study from 30 gave preference to Dextenza® therapy compared to traditional eye drops using [24].

In 2022 in USA the clinical comparison trial between OI with dexamethasone and eye drops Lotemax® to prevent sudden exacerbations of dry keratoconjunctivitis. Based on trials results OI using this therapy allows to reduce the occurrence of systemic side effects, especially increase in intraocular pressure, and has results comparable to efficiency and safety with standard eye drops [25].

Thus, despite the limited number of clinical trials, the prospects of OI as an alternative traditionally used in ophthalmology of treatment methods. Efficiency and safety of OI are confirmed not only by achieving indicators comparable, but sometimes ahead (exceeding) on quality standard therapy, but also by reducing systemic side effects, reducing treatment time with related recovery of comfort, as well as reducing the number of medical interventions, which leads to minimization the risk of medical errors and cross-contamination.

Technology of OI

Excipients used in OI development maintain controlled API release from polymeric bases for a certain period of time and modernize a dosage form in accordance with necessary technological characteristics. The most significant OI excipient is a base-forming substance which can be biodegradable or not and also have a different chemical origin (natural, synthetic, semi-synthetic) (table 2).

Table 2: Base-forming polymers in the OI development

Polymers classification	Substance examples	Commercial name, manufacturer	Range of using concentration
Natural polymers			
Alginate acid derivatives	Sodium alginate	• Protanal (DuPont) [26]	1.0–5.0 %
Chitosan	Chitosan	• Chitosan; • Poly(beta-(1,4)-2-amino-2-deoxy-D-glucose) (Acros Organics)	1.0–2.5 %
Gelatine	Gelatine	• Gelatine [27]	40.0–70.0 %
Semi-synthetic polymers			
Cellulose derivatives	• Hydroxypropylmethylcellulose (HPMC); • Ethylcellulose (EC); • Hydroxyethylcellulose (HAC); • Methylcellulose (MC); • Carboximetellulose (CMC)	• Klucel (Ashland); • Natrosol (Ashland) [24]	0.5–5.0 %
Gums	• Xanthan gum • Gellan gum	• Vanzan (Vanderbilt Minerals) [26] • Gelrite (Sisco Research Laboratories)	0.5–2.5 % 0.5–2.5 %
Synthetic polymers			
Polypolimers	• Polyvinyl alcohol (PA) • Polyvinylpirrolidone (PVP) • Other co-polymers	• Polyvinyl alcohol • PVP K-30 (BASF) [28] • Eudragit R/S 100 (BASF) [29]	50.0–60. 0% 15.0–40.0 % 7.0–25.0 %

By origin, base-forming polymers are classified into natural, synthetic and semi-synthetic. Chitosan, gelatin, and alginate acid derivatives are often used in OI development due to their following advantages– biocompatibility with API and other excipients, low toxicity and biodegradability. The main benefit of natural excipients is a pharmacological themselves effect that enhances the main pharmacotherapeutic effect of the medicinal drug [28, 30]. Currently, a great potential for drug delivery systems uses chitosan because of its good mucoadhesive properties, mainly maintain by positive charge (electrostatic attraction), which increases adhesion to mucosa, thereby providing prolonged action of the drug and its high concentration in application place [31]. Its dignity is a manifestation of a wide range of antibacterial activity, antioxidant and fungi-static action, anti-allergic properties, etc. [32]. Fulgêncio Gde O. *et al.* l were conducted *in vivo* study of the effectiveness of the OI with timolol maleate and chitosan. The experiment was conducted by comparing various methods of introduction of timolol: installation method by accumulating 0.5% of the solution of the current substance or by introducing timolol+chitosan liner in the lower conjunctival bag reed of rabbits. As a result of the study, the effectiveness and safety of using OI as an alternative treatment and prevention of glaucoma [33]. Along with chitosan OI technology as based-forming excipients, researches also include in composition alginate acid or its derivatives and their combination with different synthetic and natural polymers. The most common of them is sodium alginate, which forms ion ties with API and prolongs the local medical action [34]. The chemical structure of biopolymers are anionic polysaccharides consisting of blocks of 1.4-related residues of β-mannuronic acid and α-guluronic acid. Mohammad Sadeghi A. *et al.* were modified sodium alginate as a base-forming excipient, which causes controlled API release. After the experiment, it was found that the OI based on lipophilic modified alginate copolymer and lysenolid showed the best results for the API release duration (70% and 80% during 12 and 24 h), which is certainly an important factor in the process of controlled API delivery [35].

Synthetic polymers and copolymers are stable as fully allow to predict of technological and biopharmaceutical parameters of the medical dosage form and improve its physical properties. As synthetic polymers in ophthalmology usually use derivative acrylic (carbomers) and methacrylic acid, polyvinyl alcohol, ethylene oxide polymers and their derivatives etc [24]. The wide use of polyvinyl alcohol is associated with its stability, biocompatibility and chemical inertness, making it safe for use in various dosage forms [25]. For the treatment of glaucoma by the researchers Korol M. V *et al.,* continuing polyvinyl alcohol and sodium carboxymethylcellulose were used as base-forming agents as the result demonstrated the best rate and completeness of API release [36].

Semi-synthetic polymers used in the development of ophthalmic dosage forms include cellulose derivatives such as methyl and ethyl cellulose, carboxymethyl and sodium carboxymethyl cellulose, hydroxypropyl methylcellulose, etc. [26]. HPMC is a cellulose ester widely used in the formulation of medicines due to properties such as high biocompatibility, solubility in water, thermoplasticity and adhesion to the mucous membrane [37]. Along with HPMC, ethyl cellulose has high biocompatibility, stability (within pH 3-11), good compatibility with a wide range of excipients and most plasticizers. Due to its hydrophobic properties, EC reduces the penetration of liquid into the solid polymer matrix and, as a result, promotes the long-term release of API. Thus, ethyl cellulose-based films are characterized by good adhesion, mechanical strength and a delayed (controlled) release profile [38]. In the research of Vinod Kombat Ravindran and co-authors, a study was conducted whose main goal was to develop GLP for the treatment of glaucoma containing a combination of HPMC and polyvinyl alcohol, ethyl cellulose and methyl acrylate as base-forming agents. The study showed that the best controlled prolonged release was achieved in combination with HPMC and polyvinyl alcohol in a ratio of 1:1 (99.8% in 32 h) [39].

Excipients that contribute to an increase in the shelf life of the medical drug for example, antioxidants regulating the acidity of the substance, preservatives ensuring the safety of drug using and minimizing the possibility of side effects, can also be included in the composition of the OI (table 3).

Table 3: Excipients using in OI development

Functions	Examples	Range of using concentration
Plasticizers	Glycerine	2.0–10.0 % [26, 28]
	Polyethilglicoles (PEGs) (PEG 400, PEG 1500)	0.5-10 % [29]
pH-controlled agents	NaCl	20.0–40.0 % [20]
	NaOH	
Increasing adhesion agents	Poloxamers (Kolliphor P 188, Kolliphor P 407)	0.5–1.0 % [26]

Despite the interpretation of the Pharmacopoeia on the permissible introduction of preservatives in the OI composition development, no studies have been found for the presence of this function of excipients. For more than 50 y of existence, there have been no cases of adding excipients to the composition that prolong the shelf life of the medical drug, which makes the OI development more expedient compared to drops for ophthalmic use. It is known that preservatives are implemented into the composition of eye drops, which by their etiology negatively affect conjunctiva cells, leading to their deformation, destruction and, as a result, deterioration or loss of vision, which is a therapy in which the risk prevails over the benefit. It is also worth noting that the registered OIs does not contain preservatives in their composition and have a sufficient shelf life for sale. Especially the OI development will be relevant for unstable API compounds that are easily exposed to temperatures and other environmental factors and react with other excipients such as antibiotics, bacteriophages and biologically active substances [9].

In the pharmaceutical market, there is a tendency to create disposable packages with a composition of eye drops that does not contain preservatives, which increases the safety of the use of such medical drugs. Due to the peculiarities of the introduction of OI the dosage form initially assumes individual packaging for each insert, which frees developers from searching for solutions to extend the shelf life of the drug after the first opening, thereby shifting the focus to studying its stability during storage. Due to the solid physical state and the formation of stable complexes of a base-forming agent with an API interface the dosage form is less susceptible to the development of microbial contamination or cross-contamination inside the package compared to liquid eye forms [40].

The technology of OI production should ensure the preservation of its integrity in the process of production, packaging, storage and application. Like any ocular dosage forms, inserts must be manufactured under aseptic conditions or with the final sterilization; the decision on the manufacturing method remains with the production site and/or the patent OI holder. All manufacturing stages should be placed in clean room grade D, although this production way implies mandatory final sterilization carried out by UV radiation in industrial sterilizers. When choosing aseptic conditions for medical drug manufacturing, each stage will be carried out in rooms A classified, which provide the strictest limits of the maximum permissible number of particles in 1 m^3 of air at a certain particle size.

The technological process of manufacturing OI on an industrial scale can be represented by three stages-preparation of the base (included mixing or stirring), drying, cutting and packaging. The base preparation can be carried out in two ways: in the presence of a

solvent by mixing the components or by hot melt extrusion, where a dry or slightly moistened mixture is forced through an extruder when heated. In the first case, the API and excipients are dissolved in a solvent in a reactor with a steam jacket (if temperature is required when using a certain API) and a propeller mixer (for example, Customized IVEN-3, IVEN, China) and then poured onto prepared substrates on tapes in drying oven (for example, SHSV-3000, NPF Thermokon, Russia, BINDER GmbH, Germany) until complete solidification, after which the OI is transferred to packaging lines [41]. Such a traditional manufacturing method has limitations for large-scale production when the production of inserts by extrusion allows continuous production of economical polymer inserts.

Hot melt extrusion is a successful, universal, and continuous thermal process using in pharmaceutical manufacturing. Extrusion is carried out using such industrial equipment as the Pharma 16 twin-screw (Thermo Fisher Scientific, USA). The method is mainly used for the preparation of amorphous solid dispersions to improve the solubility of poorly soluble APIs and, thus, increase bioavailability with various methods of administration, including oral, through the mucous eye membrane and through the skin dermal. Currently, this is how the registered drug OI–Lacrisert® is produced to alleviate the symptoms of moderate and severe eye drying, as well as the medical drug Dextenxa® from intravitreal dexamethasone for the treatment of macular edema, diabetic macular edema, and non-infectious uveitis [42].

OI drying at the development stages can occur both at room temperature, but this method is not intended for further technical transfer to large-scale production or using equipment that allows switch regimes and finding optimal conditions for removing moisture [43]. As drying equipment in OI manugacturing can be used hydrators (Kitfort KT-1908, China) and thermostats (BINDER BD 56 Avantgarde. Linia, BINDER GmbH, Germany, JULABO GmbH, Germany) [44]. In addition to technologies that thermally affect the removal of moisture from the OI, equipment that provided a pressure function and the ability to dry inserts at low temperatures, which ensures the safety of trembling APIs for which temperature rise above zero is critical (for example, an API of biological origin), namely freeze dryers (crop, USA) and vacuum dryers (HETO CT/DV 60 e, Juan, Gidewang, Denmark, blade vacuum dryer Lödige Druvatherm®, Germany, Teclen GmbH, Germany) are also can be an optimal drying equipment [44, 45].

Packaging OI

Packaging of a pharmaceutical product is an important stage in the production and sale of finished dosage forms. This should not only be convenient for the consumer but also guarantee the preservation of the stable quality during the shelf life, as well as protect the contents from mechanical damage and environmental influences. For ophthalmic dosage forms, it is important to maintain the sterility of the product. The reusable packaging for OI is not possible to create since this dosage form requires compliance with sterile storage conditions that are not provided for by this type of packaging. In this regard, the best option is to use containers for monodoses, which allow not only to preserve the sterility and stability of the medical drug, but also to exclude or minimize the addition of preservatives when developing the composition of the drug and protect the OI from drying out. Thus, the most suitable type is a film contour packaging obtained from combined materials by heat welding, which includes a contour packaging without cells (strip) (fig. 4A) and a contour packaging with cells (blister) (fig. 4B). The composite material may include polymers such as polyethylene, polyurethane, polyamide, as well as aluminum foil. Such a combination of packaging components can give it additional rigidity strength and increase barrier functions (light and gas permeability) [8, 40, 46, 47].

A container-type packaging for contact lenses consisting of a rigid plastic base with a recess and closed with foil can also serve as a prototype (fig. 4C). Synthetic thermoplastic polymers, such as polypropylene and its derivatives, can be selected by manufacturers as the main material. The advantage of polypropylene is its relatively low cost, the possibility of injection molding and autoclaving [41, 45].

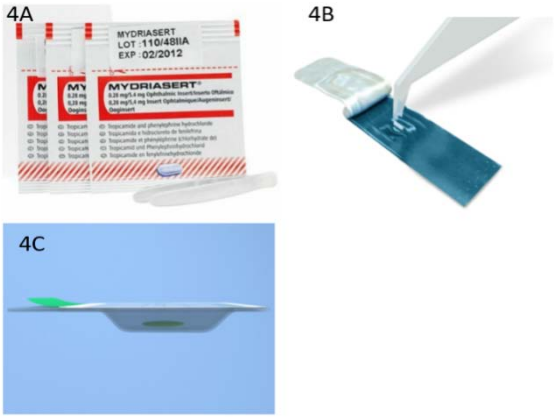

Fig. 4: Packaging OI types: 4A–Primary contour cell-free packaging of Mydriasert® [18]; 4B–Primary contour cell packaging of Lacrisert ® [19]; 4C–The prototype of a blister pack of OI by the type of container for contact lenses

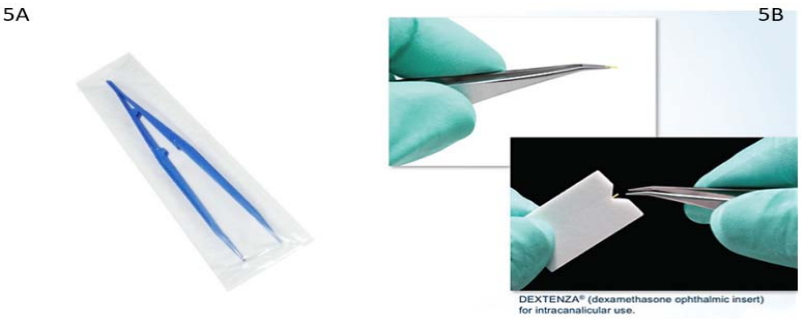

Fig. 5: Additional components of the Dextenza® packaging: 5A–applicator for the introduction of OI (tweezers) [48]; 5B–Foam insert-holder of Dextenza® [20]

To reduce the risk of microbial contamination while administrating an applicator (tweezers with a rubber tip) equipped with an external packaging in the form of a plastic container for protection from contamination and storage after use (fig. 5A) must be attached [8]. In addition, the primary packaging may also contain auxiliary elements, such as foam inserts-holders, necessary to protect the contents from destruction during movement and ease of withdrawal of the medical drug (fig. 5B) [20].

OI standardization

The choice and evaluation of quality tests is part of standardization of the finished medicinal form. In the development of medicines, researchers rely on pharmacopeia to search and analyze quality OI parameters. During the study according to normative documentation, authors usually analyze OI according to the following criteria: "sterility", "description", "size" (length, width, thickness and weight), "Uniformity of dosage units", "dissolution", "moisture loss", "moisture absorption" and "dissolution time", "pH". However, the above parameters will not be able to fully identify the OI quality, as they do not take into account all the features of its application, namely, placing it on the lower eyelid, where the contact of the drug with mucosa cells. Therefore, the OI development is also accompanied by research parameters "adhesion", "strength in folding", "tensile strength" and an irritation test (HET-CAM test) [49, 50].

For testing the moisture absorption by exposure to them the water environment of pre-weighed inserts were immersed in the tablet containing a phosphate buffer at 37 °C. The samples were removed from the phosphate buffer through equal time intervals and re-weighed after excess surface solution with filtration paper. The parameter was calculated by formula:

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight (g) - Initial weight (g)}}{\text{Initial weight (g)}} \text{ x } 100\ \%$$

To determine the stability of OI in dry and wet conditions a certain amount of each insert was placed in an exicator containing calcium chloride and aluminum chloride with humidity of 79.5%. Three days later (72 H), inserts were removed from the exicator, weighed again and determined the percentage of moisture loss by following formula:

$$\text{Moisture loss (\%)} = \frac{\text{Initial weight (mg) - Final weight (mg)}}{\text{Initial weight (mg)}} \text{ x } 100\ \%$$

OI test on the "adegisiveness" is the main quality parameter due to the fact that its results demonstrate the effect of contact of the insert with the eye mucosa, based on which the degree of bioavailability and completeness of API release from the local insert action. Adhesive properties were determined by mechanical method, i.e. determined the load that the system can withstand in the experiment on the passage. To determine the samples adhesion of as a mucous surface model was used a mucin solution in 20 % concentration which covered with the gauze surface. OI samples have 4.5 x 2.0 sm performed the adhesive role. The effort determined the OI, weighing the load in which the moment of passage was fixed.

To check the irritation degree of the eye mucosa is conducted HET-CAM test (a test for chorioallantoic membrane). The essence of the method is as follows: fertilized chicken eggs mass 50.0-60.0 grams without defects incubate at 37±0.5 °C within 3 d periodically inverting, then in equatorial position on the shell make a hole 2x2 sm in such a way that the chorioallantoic membrane is visible on which the OI is placed.

One of the quality tests of bio soluble inserts is "biodegradation". This indicator characterizes the ability of the OI to dissolve in a liquid environment for a certain period of time. As an environment used by researchers for dissolution is a solution that simulates "artificial tear" (pH=6.8), or liquid specified in the relevant normative documentation. Measurement is carried out by decayability test where in each of the six tubes placed on one sample from selected samples. After that the basket of the device is lowered into the vessel with liquid and explores the condition of the OI after a certain period of time. The sample is considered to be completely dissolved when there are polymers that have been totally disintegrated or there is a soft mass that is destroyed by a light touch of glass stick [44].

It is also important to mention the dissolution test to determine the amount of API that must be released in the dissolution environment for a certain period of time. This parameter is particularly a significant criterion for assessing biopharmaceutical properties of medicines with modified and controlled release [46-51]. In their works, researchers use one of the 3 methods of " dissolution test":

1) *Frantz diffusion cell.* The cell consists of two parts: donor compartment containing the test sample, and the release cameras with the receptor environment (phosphate buffer solution pH 7.4), where two parts are divided by a membrane provided contact with the environment for diffusion and release of API from sample. The Franz cell is placed in the water bath to maintain temperature within 37 °±1 °C, also for mixing the buffer solution, a magnetic bag is provided. The sample diffuses through the membrane into the receptor chamber, from which in the future occurs sampling with filling the receptor environment. Further sample testing is carried out by spectrophotometry methods [34, 52].

2) *"Rotating basket" device.* The device consists of a vessel for dissolving with a hemispherical bottom, engine with speed regulator and mixing element consisting of a vertical shaft attached to the bottom of the cylindrical basket. The volume of the dissolution environment is usually 500 ml, and the rotation speed of the basket– 100 rpm. For comparative kinetics of dissolution in the case of OI as the environment is used "artificial tear". During the experiment, the sampling is carried out, which is analyzed using a spectrophotometer [51, 53].

3) *Dialysis through a semi-permeable membrane.* The device consists of an outer glass vessel–thermostatable glass and inner vessel without a bottom-dialysis tube with the most using cellophane film as a semipermeable membrane. OI is applied to the membrane, fixed on the dialysis tube, then the installation is made into the receptor environment of the outer vessel. The tube base should be immersed in the liquid not more than 2 mm. In the case of ophthalmic dosage form, the receptor environment serves as "artificial tear" or water purified. The glass with tube thermostat at constant temperature of 37 °±1 °C. Sampling is carried out at equal intervals with filling of the receptor environment and analyze with spectrophotometric methods [52, 54, 55].

CONCLUSION

Summing up, at the moment only 4 OI medicinal products are officially registered on the global pharmaceutical market; diverse clinical studies are being conducted aimed at studying the compliance and effectiveness of the insert as a preferred dosage form over traditional eye drops therapy, increasing the accuracy of API dosing and minimizing cross-contamination. It should also be noted the simplicity of the OI technological process, the stages of which can be validated according to actual legislative requirements, both in small-scale production and in industrial manufacturing to bring the medicinal drug to the market. The composition development and its assessment of quality parameters testing not only according to the Pharmacopoeia, but also not included in it, for optimal API release and the therapy safety, is actively carried out by researchers around the world. Thus, the development of OI is a promising area of research for pharmaceutical companies and scientists engaged in improvement of ophthalmotherapy, both on the part of the patient and on the part of the manufacturer.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest.

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