International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 5, 2022

Review Article

APPROACHES TO THE SEARCH OF THE OPTIMUM PACKAGING OF EYE DROPS

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Received: 26 Apr 2022, Revised and Accepted: 03 Aug 2022

ABSTRACT

The purpose of this study is to find a unique ophthalmic packaging that takes into account modern requirements for both maintaining the quality and safety of the drug, compliance with therapy, and increasing the profitability and environmental friendliness of its production. Statistics from open international databases on drugs approved for ophthalmic therapy in 2022 are provided. The research criteria were a valid registration status, the type of packaging and the presence of a preservative in the composition of the eye drops. The results of statistical processing of databases of ministries of health of different countries have shown the relevance of monodose ophthalmic packaging, capable of long-term storage of the drug without preservatives. In many countries, particularly in Europe, many drugs in the form of a monodose containers are registered. On this basis, a unique aluminum-based monodose container design is proposed, eliminating the use of large quantities of plastic.

Keywords: Ophthalmology, Packaging, Adherence to treatment, Compliance, Pharmionic

DOI: https://dx.doi.org/10.22159/ijap.2022v14i5.45402. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Eye drops are currently the most sought-after active ingredient administration in ophthalmic practice due to many years of experience in its use and the simplicity of the technology [1]. Alternative dosage forms-eye, ointments and gels, eye films, including lenses containing active substances, eye implants (for example, for intravitreal injections) and microcapsules for placement in the lacrimal canal are not widely used due to the high adherence of patients and doctors to traditional liquid dosage form intended for instillation into the eye [2, 3].

At the same time, most ophthalmologists note the low accuracy of self-instillation of eye drops by patients, which can lead not only to a violation of the dosing regimen and the volume of the therapeutic load but also to microtrauma of the cornea and cross-contamination [4].

The prototype of modern eye drops was "colliria"-solutions of active substances of plant or mineral origin in water, egg white or animal milk commonly used in medicine since ancient Greece and ancient Rome [5].

As part of the technology improvement process, changes have been made to the packaging and distribution of eyedrops. Mainly for the purpose of improving the usability and determination of the accuracy of the dosage, as well as to maintain the sterility of the form throughout the period of application.

The sterility requirement for eye instillation solutions was first documented in 1955 in the American Pharmacopoeia. However, back in 1947, Robert Alexander and William Conner's small manufacturing Alcon pharmacy specialized in ophthalmic solutions and produced sterile eye drops by treating the finished product with hot steam. Afterward, with expanding production, pharmacists Alexander and Connor created Alcon Laboratories Inc., the company which remains the leader in the industry for the production of ophthalmic drugs, contact lenses and eye implants [6].

An article by M. J. Hogan [7] from 1949 was one of the first to emphasize the need to preserve the sterility of the product in the only multidose eye drops available at that time by adding specific bactericidal agents. The study noted the potential prospect of using benzalkonium chloride as a preservative quaternary ammonium chloride synthesized in 1935 by Gerhard Domagk, head of the development department of I. G. Farbenindustrie, the largest chemical-pharmaceutical concern at that time [8].

Until the beginning of the 21st-century benzalkonium chloride, among other antimicrobial agents, was widely used in the technology of ophthalmic dosage forms, both to separate reports of its negative effect on the course of eye diseases (glaucoma) and the condition of the visual organ were combined into an evidence base for its local toxicity [9-13].

Thus, since the beginning of the 2000s, the world scientific community has been solving two main problems regarding the technology of ophthalmic liquid dosage forms-increasing the correctness of instillation of the drug by the patient and the accuracy of dosing the drug, as well as finding ways and possibilities to maintain the sterility of the pharmaceutical product without the use of locally toxic preservatives.

The solution to these problems could be find in the search for optimal modern packaging solutions-multidose and monodose containers made of various materials. This search was conducted within databases of registered medical products in different countries Finland, Sweden, Germany, France, Russian Federation, Spain, China, Singapore, USA and Malaysia. The criteria used in searching of ophthalmic drugs were the registered status of the product, the type of doses (monodoses or multi doses packaging) and the preservative's presence in the eye drops formula.

Preservatives in eye drop technology

Compounds from the groups of quaternary ammonium components, parabens, alcohols, amides, and mercury compounds have traditionally been used as preservatives for ophthalmic preparations [9]. The most used in pharmaceutical compositions are benzalkonium chloride, polyquad (polyquaternium-1, PQ-1) and cetrimonium chloride [14].

Currently, the negative effect of benzalkonium chloride on the state of the visual organ has been most studied.

In the study [15] it was proved that benzalkonium chloride exhibits toxic properties at the cellular level and inhibits the mitochondria of human corneal epithelial cells [15, 16]. The degree of negative impact on the structures of the eye apparatus depends not only on the frequency of use of the drug containing this excipient but also on

the concentration of the preservative. A recent study demonstrates that with frequent use of preparations with a high content of benzalkonium chloride, toxic effects are manifested; in turn, a reduction in instillations or a decrease in the amount of excipient leads to a minimum or absence of negative side effects [17].

In addition to studies on the toxicity of benzalkonium chloride, recent experiments reveal adverse effects of the preservative poly quad. These studies show that this excipient has a negative effect on the integrity of the cell membrane and induces cytotoxicity in the cells of the ocular surface [18]. The main disadvantage associated with this preservative is its tendency to reduce the density of conjunctival caliciform cells, thereby reducing the formation of the aqueous sequence of the tear film.

Currently, manufacturers are increasingly refusing to create drugs with preservatives to eliminate the undesirable consequences of the treatment of eye diseases. Clinical studies of drugs with and without preservatives used in the treatment of glaucoma, bacterial conjunctivitis and dry eye syndrome confirm the effectiveness of treatment without preservatives [19-22]. The advantages of such drugs are the reduction of adverse and allergic reactions, which leads to greater patient compliance, as well as the possibility of their therapy for young children.

However, a large volume of eye drops packages (more than 5 ml) for multiple uses of medicines does not always allow maintaining the sterility of the solution for a long time if there are no preservatives in the composition itself [23].

Shortly after the worldwide trend to phase out preservatives in ophthalmic solutions, there were reports of cross-contamination of eye drops in multidose packs. In 2006, similar studies were carried out in large clinical centers in the United Kingdom, the United States and Kenya [24-26]. Studies have shown that more than 8.0% of ophthalmic solutions used in long-term care facilities are contaminated with bacteria. Also, in the study [27], the effect of the active ingredient on microbiological stability was noted. Contamination levels have been shown to range from 0% for antibiotics, 20% for local anaesthetics, and 40% for povidone-iodine, and solutions containing steroids were 5.8 times more likely to be contaminated than non-steroidal solutions [16].

In 2019, a study [28] conducted at the Department of Ophthalmology, Jimma University Specialist Hospital (JUSH), Southwest Ethiopia, was published. This study is demonstrated an extremely high level of contamination of eye drops (72.8%), including antibiotic-resistant microorganisms. In most cases, the tip of the dropper bottle was subjected to microbial contamination in contrast to the contents of the bottle, which led to cross-contamination of the instilled liquid and the patient's eyes.

Correct instillation by the patient

As already noted, the second significant problem in the development of modern ophthalmic solutions is incorrect instillation of the drug which reduces dosing accuracy and increases the risk of cross-contamination with the vial tip.

In recent years, more and more attention has been paid to teaching patients the correct technique for instilling eye drops [29, 30]. Patients with glaucoma and increased intraocular pressure often become the objects of pilot studies in this area [31, 32]. For example, a 2021 University of Michigan (USA) Medical School study evaluated the impact of a personalized Support-Educate-Empower (SEE) glaucoma training program on eye drop technique and eye drop self-efficacy. Eye drop administration was videotaped prior to the first face-to-face SEE coaching session consisted of training in eye drop techniques using a motivational interviewing approach. The study carried by da Costa *et al.* [33] has shown that the SEE coaching program significantly reduced eye drop bottle contamination and increased the self-efficacy of eye drop instillation [29].

A significant contribution to the risk of cross-contamination is made not only by the human factor but also by the design of the vial tip. The study showed that adjusting the instillation angle of eye drops to 90° as well as using a nozzle geometry that prevents the solution from flowing onto the vial wall significantly reduced the level of contamination (from 53.7% of cultures when instilling drops at 90° to 70.4 % cultures at 45°. The researchers concluded that standardizing dropper bottles and adjusting the angle of instillation could reduce contamination levels and critically affect the quality of therapy.

Modern types of primary packaging for eye drops

Although due to the trend towards eliminating preservatives in the composition of ophthalmic solutions, the type and material of packaging plays a significant role in maintaining the sterility of eye drops and minimizing the risk of microbial cross-contamination. Manufacturers are pursuing two strategies in parallel, there are the use of multi doses packaging and the use of monodose containers for eye drops (fig. 1).

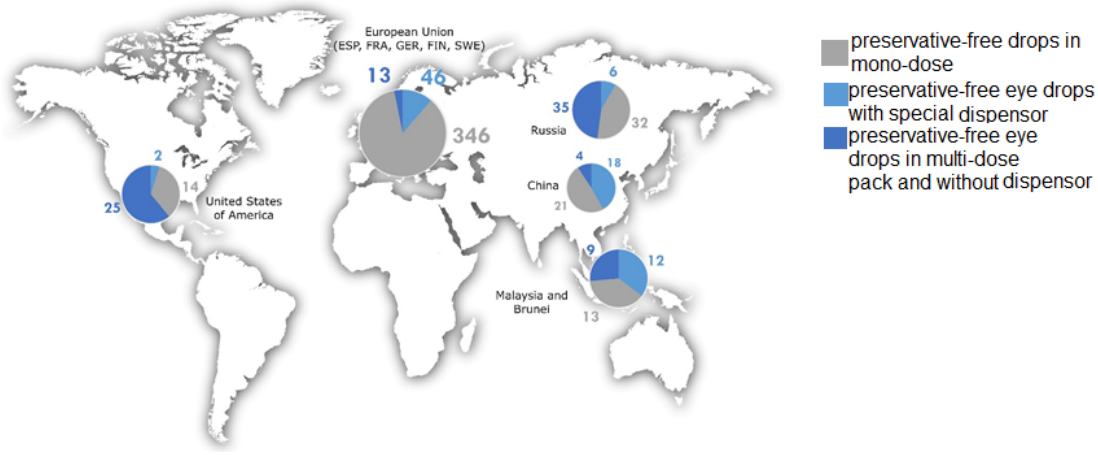


Fig. 1: Number of registered preservative-free ophthalmic preparations in monodoses and multidoses forms in various countries

According to the analysis of local and international state registries of registered medicines, the share of ophthalmic preparations that do not contain preservatives averages 20.0%. Among European countries, the leader in the transition to preservative-free eye drops is Sweden (38.7%). On average, the proportion of preservative-free products registered in the European Union is higher than in the USA, Asia and Africa.

The use of monodose packaging prevails over the introduction of special dispensers that prevent cross-contamination of multidose containers. Only the market for liquid ophthalmic formulations in Hong Kong (China) represents more than 40.0% of medicines in multidose packs, while monodose packaging is typical for more than 90.0% of all drugs in the form of eye drops in the German and Swedish pharmaceutical market.

Multidose packaging

Multidose ophthalmic solutions are a type of primary packaging familiar to the patient that is more environmentally friendly compared to polymer monodose containers. At the same time, the regulation of the number of doses produced is carried out by the patient independently and can be adjusted according to the indication.

Modern multidose containers for eye drops should ensure the correct self-instillation, control the uniformity of the volume of the released dose and prevent cross-contamination of both the contents of the vial and the dropper tip.

In modern multidoses, contamination prevention can be achieved in two ways:

- Using the original design of the bridge in the tip coated with silver and prevents the penetration of microorganisms;
- With the use of sterilizing filtration of the incoming air (filter with a pore size of not more than 0.2 microns), which design ensures the sterility of the medicinal product during storage and use.

One of the first multidose systems with a device to prevent secondary contamination of a pharmaceutical product was ABAK® (Thea Laboratories) patented in 1989. The pilot series of systems was not a preservative-free product but contained a microporous liner that removed the preservative prior to instillation. Subsequent modifications to the system included a silver mesh around the dispensing port. Currently, the preservation of dose sterility is based on sterile filtration of eye drops through a special microporous pad and a hydrophilic membrane. In accordance with this fact, the recipe does not contain preservatives in the current version [34].

Similar to the ABAK® system the design and method for preventing cross-contamination of eye drops are used by Ocutears® (i. com medical GmbH, Germany), Novelia® (Nemera, France), Aptar® (Aptar Pharma, Switzerland). For instillation as in traditional BFS dropper bottles achieved using BFS technology (blow-fill-seal), uniform compression of the bottle walls is required, which can reach 10-20 N [35].

An alternative to such systems in terms of liquid dosing is the COMOD® system (Ursapharm, Germany) patented in 1994 [36]. Pilot tests of the antibacterial resistance of the preservative-free form in the new package showed that most patients coped well with self-instillation of KOMOD® regardless of gender and age, and the system itself is an adequate microbiologically safe container for eye drops without preservatives.

In 2006, ophthalmic preparations entered the market in a similar primary package the Aero Pump 3K® system (Aero Pump, Germany). In both of these systems, the liquid in the outlet is protected from microbial contamination by a silver wire located near the outlet tip. The liquid pharmaceutical composition is placed in a polymer bag inside the bottle (similar to the popular Bag-On-Valves aerosol medicinal systems), protecting it from contact with atmospheric air. The volume of the dose in such systems is not controlled by changing the pressure in the polymer bottle (as is the case with BFS dropper bottles), which allows standardizing the therapeutic load. Instillation by pressing the piston of the bottle bottom is simple, does not require much effort (about 7-10 N) and it is available to patients of any age [37].

Monodose packaging

To date, the most widely used preservative-free eye drop technology is the monodose BFS droppers. Medical products in such packaging are common in Europe, including the Russian Federation, which is different in the United States and China (table 1).

Table 1: Quantity of registered monodoses in several countries

Part of the world	Country	Quantity of registered monodoses
Europe	Germany	148 [38]
(Western, Northern, Eastern and Southern parts)	France	77 [39]
	Sweden	67 [40]
	Russian Federation	52 [41]
	Spain	38 [42]
	Finland	33 [43]
East Asia	China	23 [44]
Southeast Asia	Singapore	18 [45]
North America	USA	14 [46]
Southeast Asia	Malaysia	6 [47]

This technology began to be used in the packaging of ophthalmic liquid products in the 1970s. The volume of one dose in BFS droppers varies from 0.3 ml to 13.0 liters. However, it should be noted that the process requires a significant overflow of bufus, which makes a monodoses much more expensive compared to multidose dispensers [37]. Such monodoses are convenient for transportation because they are light and allow the patient to divide the required number of doses for daily instillation. Nevertheless, the opening of such droppers may be difficult for both elderly patients and patients with impaired coordination and vision. In addition, the use of such packaging leads to a significant increase for plastic waste and requires the creation of a program for their recycling or disposal. Because of the point mentioned above the further development of monodose technologies requires a revision and adjustment of approaches to the choice of packaging materials.

Packaging materials

There are a large number of companies involved in the development and implementation of new technologies for packaging medicines on the market. Manufacturers are striving for the rational use of packaging materials to reduce production costs and improve product quality [48]. One of the most important requirements for packaging materials is the protection of the drug from exposure to light, atmospheric moisture, oxidation, microbial contamination [49, 50] and what is also important the formation of drug compliance [51-53]. In this regard, the trend towards the development of innovative pharmaceutical packaging is steadily growing [54]. For example, the volume of the global market for ophthalmic packaging was estimated at 7.1 billion US dollars in 2018 and, according to forecasts, by 2026 it will grow by an average of 9.9% [55].

Nowadays, a wide range of solutions made from various materials represents the market of packaging materials for eye drops. According to the statistic [56], type I and type III glass as well as polyethylene (PE) and polypropylene (PP) are used as packaging for eye drops. Glass has traditionally been used in pharmaceutical technology, but it has the disadvantages of brittleness, inconvenience in use and high cost, which is why it is quickly replaced by plastic. Therefore, plastic packaging accounted for the largest market share in 2018. In many respects, this became possible due to the Blow-Fill-Seal (BFS) technology, where low-density polyethylene (LDPE) is widespread (fig. 2) [55, 57].

LDPE is extruded at a temperature of 170–220 °C because of which thermal energy can be transferred to the contents of the package, which is a critical factor when packaging thermolabile drugs [59]. Furthermore, it is believed that it is difficult to label BFS-produced packaging [60] and that the equipment requires special arrangements to avoid emergencies associated with the ejection of

polymer particles [61, 62]. In general, plastic as a material also has its drawbacks, namely, vapor permeability, instability to steam sterilization, the requirement to be known to be sterile and free from mechanical impurities, and the production of special equipment for their closure for bottles [56]. Recycling of such packaging also remains an open question as global plastic production in 2019 reached 400 million tons, while the volume of biodegradable plastics obtained from renewable resources amounted to only 3.5 million tons, i.e. about 1% of the total production [63, 64].

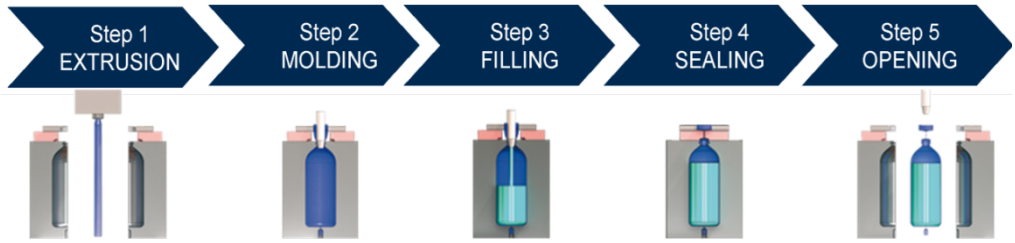


Fig. 2: BFS technology [58]

In this regard, the most promising is film contour packaging, obtained based on combined materials by heat sealing which includes cell-free (tape) and cell (blister) types of packaging. According to reports, the average annual growth rate of the blister packaging market for 2020-2028 will be 3.96-5.70% [65] and by 2026 the global blister packaging market will reach 16630 million US dollars compared to 15760 million US dollars in 2020 [66, 67], which indicates its prospects and demand among consumers. The most important reason for the introduction of blister packaging is the close to perfect protective functions of the material. The formation of a multilayer structure with the inclusion of aluminum foil (ALU) in it makes it possible to improve the performance of the material associated with light and gas permeability. Moreover, ALU laminating has been proven to add rigidity to the structure, reducing not only the size of the product but also the raw material costs of its production. It is also inextricably linked to avoiding the diffusion of contaminants into the drug product, where primary polyethylene terephthalate (PET) can serve as an effective barrier. PE does not have the same strength properties as PET but it is also capable of sealing and has a lower cost. Additionally, both PET and PE can serve as release layers in composite material and exhibit antistatic properties to prevent the material from building up a charge. Oriented plastic films such as oriented polyamide (OPA) have even better barrier, mechanical and optical properties. Furthermore, primers and adhesives both are used in the production technology of composite materials the task of which is to improve adhesion between layers [68]. The most popular in this case is a polyurethane (PUR) [69]. As a result, Amcor and Rohrer AG developed the Frangible Formpack® Blister (DosePan), a sterile blister made of two types of composite material, including an aluminum base (fig. 3).

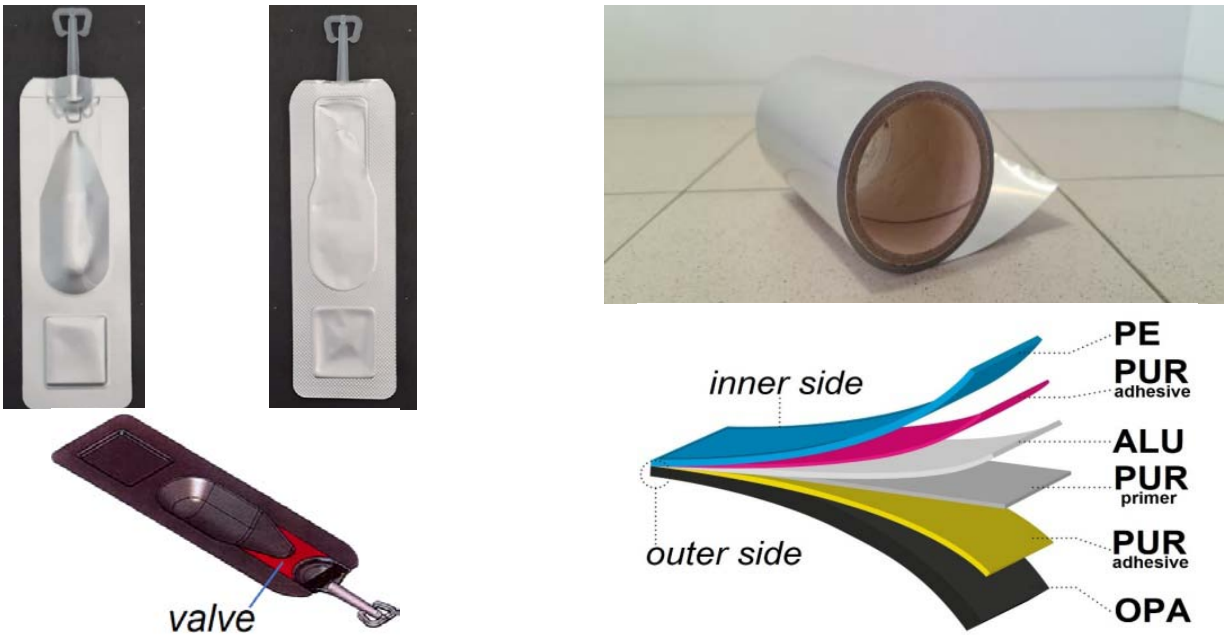


Fig. 3: Frangible formpack® blister (DosePan) and composite material

This solution can be used in many dosage forms including ophthalmic dosage forms as drops or ointments [70]. For the production of such blisters, special blister machines are used existing industrial and pilot versions. The R560 Servo is designed as a modular design, where each module is responsible for performing on a separate stage of the process. A servomotor acts as a drive for such a device is the basic principle behind the creation of the Frangible Formpack® Blister (DosePan), which is to thermally bond the base to the top, while the heated modules are cooled by external cooling devices.

The complete blister production cycle consists of 6 technological stages: cutting, cold forming, spout sealing, filling and fragile sealing, permanent sealing and final cutting (fig. 4).

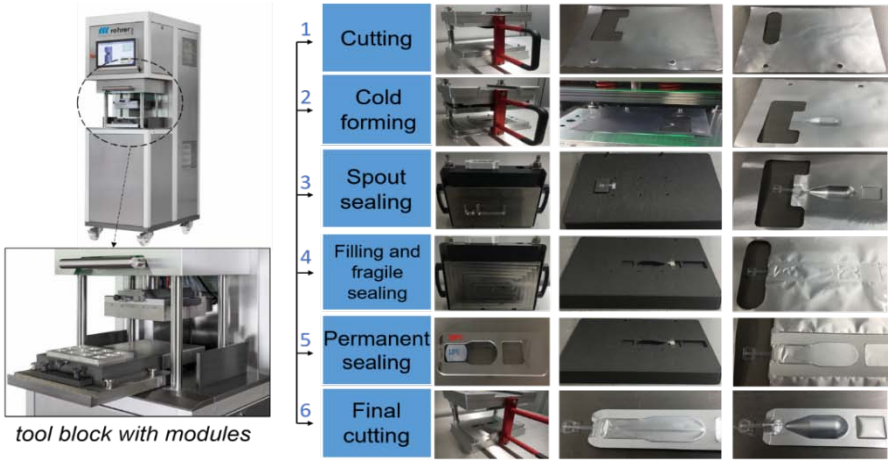
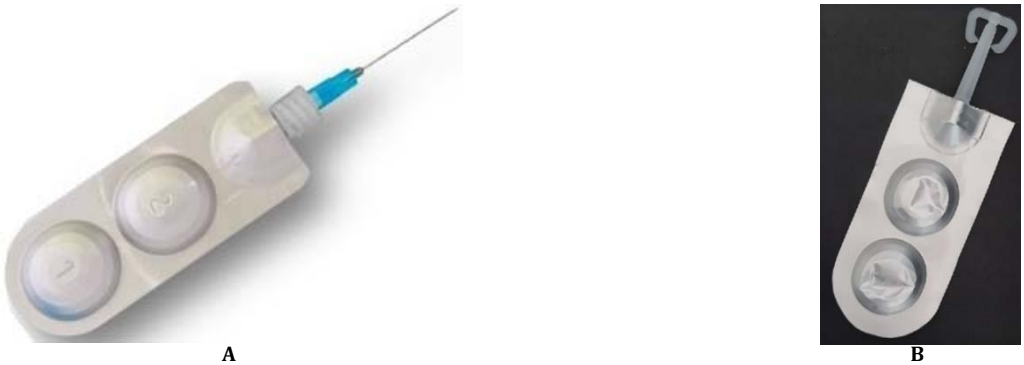


Fig. 4: Rohrer R560 servo and frangible formpack® blister (DosePan) production steps

Cutting involves the transformation of the composite into billets (base and upper part) with their subsequent positioning, after which holes of a certain shape and size are formed in the material. This is followed by cold forming, creating a cell for the drug using a module with guide columns, an established form of stamping punches, a stamp plate with locking screws and compression springs, a retainer and a stamp. Moreover, the module clamps the composite between two plates while appropriately positioned punches pull it into the required shape. After the cell is created, the spout is sealed, which is a dosing device for the drug. The spout is sealed at 180 ℃ using a sealing module with an installed plate undergoing heating and a base part with a mold for sealing the spout. During this stage, the spout is located in a niche and then a billet (base) is applied on top. Having at the output a billet with a cell and a dosing device, the stage of filling and brittle sealing follows. This operation is carried out using a sealing module with a fragile sealing plate and a base part with a fragile/permanent sealing mold. On the base part there is a billet with a cell and a spout, which is to be filled with the drug. Following this, a top film is applied to the billet with the preparation, and at 140 ℃ a fragile sealing occurs. Potentially important is permanent sealing, during which a valve is formed between the spout and the cell containing the drug. In permanent sealing, a special module is involved, which has a cooled rod in its design. On the form of fragile/permanent sealing, there is a billet with the preparation, which is subsequently subjected to permanent sealing at a temperature of 190 ℃. The presence of a rod separately cooled to 10℃ contributes to the formation of a temperature difference in the working areas, due to which a valve is formed between the spout and the cell with the drug. It is important to note that the absence of heating in the area of the cell with the drug favorably distinguishes this concept in the production of thermolabile drugs from the BFS technology. At the final stage (final cutting), a sterile blister is formed.

There are ophthalmic medicines that are not stable when stored as aqueous solutions. These medicines include, for instance, Lifferon® and Poludanum®. It is known that in order to increase the stability of such drugs and extend their shelf life, lyophilization is often used as a result of which lyophilized powders are obtained, the solutions of which are prepared with special solvents immediately before administration [64]. Nevertheless, this causes certain difficulties for the end user since before taking the suspension must be prepared and in addition, it is recommended that the preparation of the drug be carried out by specially trained medical personnel. For such purposes, an innovative multi-chamber blister system Dual Chamber Blister® was developed (fig. 5).



A **B**

Fig. 5: Dual chamber blister® in different types: for retrobulbar injection (A) and for instillation (B)

Mixing in the Dual Chamber Blister® occurs due to the mechanical deformation of the internal seal between the two cavities, where one of the cavities contains the solvent and the second lyophilisate. At the same time, tightly closed areas around the rest of the blister prevent leakage of the medicine, which is because of the characteristics of the material used and the heat-sealing technology. Thus, such a system improves drug stability and optimizes logistics by eliminating the need for controlling storage temperatures and glass/polymer containers, which have several disadvantages.

CONCLUSION

Appropriate use of drugs is a prerequisite to effectiveness and safety. In this aspect, most ophthalmologists note low compliance of ophthalmic dosage forms, which can lead not only to a violation of the dosing regimen and the volume of the therapeutic load but also to microtrauma of the cornea and, most dangerously, secondary microbial contamination. The latter is more relevant for preservative-free medicines, where monodose packaging is designed

to avoid the risk of infection of the ocular surface with pathogens. To date, the most widely used technology is BFS droppers, but questions remain related to the possibility of producing thermolabile drugs in this way, the feasibility of using polymers in its production, and subsequent disposal. Developments in this area have created a new concept in the packaging industry, based on the use of an ALU-based composite.

DosePan® as an alternative to other packaging solutions could help the ubiquity of this technology, and a large-scale transition from traditional glass/polymer packaging to composite blisters based on an ALU layer is expected. Furthermore, depending on the product and target group, the opening mechanism can be adapted to the respective application, and there is a greater degree of freedom in the choice of color and packaging printing, which will improve drug compliance.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

Declare none

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