REVIEW ARTICLE

Prospects of Using Biopolymeric Films in Medicine and Pharmacy

N. V. Khokhlenkova[1], O. V. Palii[2], O. V. Andrieieva[2], A. D. Verovskaya[1]

[1]Department of Drug Technology, National University of Pharmacy, Kharkov, Ukraine, [2]Department of Therapeutic Dentistry, Kharkiv National Medical University, Kharkov, Ukraine

Abstract

Introduction: Nowadays, biopolymers and biomaterials are an actively developing field, interesting both for specialists from various fields of science and for society at large. The range of polymers of both natural and synthetic origin is constantly expanding, but only a few of them are used in pharmaceutical production and medical practice. Due to the composition of polymers and active pharmaceutical ingredient, films are a promising form for applying in dentistry, ophthalmology, surgery, and other fields of medicine. **Materials and Methods:** In the work marketing and economic research methods are used to ground social and medical practicability of developing new dental products for local treatment. **Results and Discussions:** Based on the data of modern scientific literature, the requirements for medicinal films are outlined, their classification is given. Approaches to the choice of active and auxiliary substances in the process of developing new film formulations are described. The prospects of using films in surgery, dentistry, ophthalmology, and dermatology are shown. **Conclusions:** Based on the review, polymer films have been classified, and the requirements for the given dosage form have been defined. Approaches to selecting active and auxiliary ingredients have been considered. The main aspects of the technological process for the preparation of films are described. The ways of rational application of films in medical practice have been highlighted.

Key words: Biopolymer, films, inflammatory dental diseases, wounds

INTRODUCTION

Nowadays, biopolymers and biomaterials are an actively developing field, interesting both for specialists from various fields of science and for society at large. The range of polymers of both natural and synthetic origin is constantly expanding, but only a few of them are used in pharmaceutical production and medical practice. However, the advantage of most polymers is having not only formative but also biologically active properties, long-acting, increased bioavailability of low soluble compounds, and expanding the period of validity of medications. All above mentioned determines the possibility for developing medications based on polymers of different nature and structure for applying them for various pathologies and at different stages of development of the pathological process.[1]

Developing new medications with active pharmaceutical ingredients immobilized on polymer carriers - films – which are used in various fields of medicine - is becoming more and more popular.[1-4] Films are solid or soft preparations of a suitable size and shape consisting of a matrix in which the active ingredient is incorporated or an active substance surrounded by a membrane controlling the release rate. Medicated films are the application dosage forms and intended to introduce active substances into the body through the skin, periodontal tissue, or mucous membranes.

Due to the composition of polymers and active pharmaceutical ingredient, it is possible to achieve a prolonged effect of the pharmaceutical substance, minimal traumatization of the wound surface, an increase in the healing rate of pathological sites, a significant dose reduction and reduction of the consumption of medications. Films are easy to apply and have a wide range of pharmacological effects. Thus, films are a promising form for applying in dentistry, ophthalmology, surgery, and other fields of medicine.

Address for correspondence:
N. V. Khokhlenkova, Department of Drug Technology, National University of Pharmacy, 4, Valentinivska Street, Kharkov, Ukraine. E-mail: hohnatal@gmail.com

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The purpose of the work is carrying out the analysis of classification, nomenclature, and advantages of applying medicinal films; approaches to selecting active and auxiliary substances, as well as to the technological process of developing them.

MATERIALS AND METHODS

In work the retrospective, logical, analytical research methods have been used to analyze the data of special literature and regulatory framework. The current review supports the updated systemic information on the use of biopolymeric films. We selected pre-reviewed papers on biopolymeric films and their uses shown on scientific database Medline, Scopus, Science direct, Blood Journals, Springer link, Wiley, Oxford journal, and Google Scholar. The following keywords were used to search for the literature inside the databases are biofilms, Pharmacy, and natural product.

RESULTS AND DISCUSSIONS

According to the nature of the effect on the body, medicated films can be of a general (oral, rectal, transdermal, and intravascular) or local action (intraocular, intravaginal, for application to skin and wound surfaces, and mucous membrane of the oral cavity).

Furthermore, polymer films are divided according to their pharmacological effects: Anesthetic (anilocaine + chlorhexidinebigluconate), (anilocaine + dioxidine); remineralizing (calcium chloride + potassium phosphate disubstituted + sodium fluoride + chlorhexidine bicarbonate); immunomodulating, stimulating the function of the central nervous system, or basic metabolism, anti-stress (ginseng, may chang, *Eleutherococcus*, and magnolia vine); calming (valerian and motherwort); anti-inflammatory, antiseptic, astringent, antiallergic (milfoil, cinquefoil, chamomile, sage, plantain, violet, bee glue, romazulan, erucond, moomiyo, and aekol); and vitaminizing (rose hips).[5-10]

Having such a diverse range of effects, polymer films are an excellent substitute for most modern bandages, analogs of which are hard to find.

The technology of medical films is quite simple and involves using polymers of natural, semi-synthetic, or sometimes synthetic origin, which are able to form hydrogels, and when they dry an elastic water-soluble film is formed.

Nowadays, biopolymers are understood to be high molecular compounds synthesized with living organisms and consisting of a single type of macromolecules. Biomaterials are understood to be any substance, natural or synthetic, from which the biomedical system consists entirely or partially. Biomaterials include biopolymers, used not only in medicine but also in other industries, as well as non-biodegradable polymers for the biomedical purpose. Biodegradable polymeric materials can be divided into three groups:

1. Polymer materials based on natural biopolymers: Natural rubber, proteins, polysaccharides, polymers from unsaturated vegetable oils, lignin, pullulan, etc.;
2. Polymer materials synthesized chemically from microbially produced monomers and oligomers. Polyhydroxyalkanoates (with *Alcaligenes eutrophus*, *Rhodococcus* sp., *Chromobacterium violaceum*, and *Pseudomonas putida* bacteria); polylactide - an intermediate product of microbial fermentation of agricultural and food waste containing carbohydrates - are synthesized microbiologically; cellulose can be obtained from low molecular glucosides when exposed to microorganisms of the Acetobacter, Sarcina ventriculi, and Lampropedia hyaline family;
3. Composite materials, which are mixtures of various polymers, such as ethylene-vinyl acetate copolymers, ethylene-propylene copolymers, ethylene-vinyl alcohol copolymers, ethylene-acrylic acid copolymers, linear polyurethanes, and polystyrene; cellulose diacetate with starch, chitosan, and polyvinyl alcohol.[11]

Composite materials are used most often since they are more economically available. Based on these combinations, polymer films are obtained, which in their turn are divided into the ones used in the finished form and the ones formed directly on the wound surface. The films of the first group include polyethylene, polypropylene, polysiloxanes, polyvinyl chloride, poly ethyl acrylate, and silicone. Along with hydrophobic polymers, hydrophilic films insoluble in wound exudate are used, for example, copolymers of a acrylate with vinyl acetate and other monomers, or films of polyvinyl alcohol and polyvinylpyrrolidone.[12,13] Isolation films of the second group, formed directly on the wound surface, are represented in the form of aerosol compositions, when applied to the wound for 1–2 min, due to evaporation of the solvent, a dressing is created in the form of a film.

Requirements

To develop a new and modern medication, it is necessary to take into consideration the requirements imposed directly on it. Films are no exception. The main requirements they should meet are the following:

- Microbiological purity or sterility of the finished product, which must be maintained to prevent introduction of infection to the affected area or contamination of environmental objects;
- Remove effectively excess wound exudate and its toxic components, ensure optimal therapeutic effect with minimum of side effects, stability of ingredients in the production process;
- The accuracy of dosing and the uniformity of the biologically active substances concentration for a long time;

- Constructive simplicity and technological capabilities to produce;
- Strong fixation onto the moist and hard tissues of the mucous membrane of the oral cavity and wound surfaces with saving anatomical and physiological properties of the skin and oral mucosa;
- Good gas permeability for the normal course of reparative processes;
- Observance of hygienic standards of the parotid fluid's pH (in dentistry);
- Saving physical and chemical parameters and concentration of medicinal products within 2 years;
- Pain syndrome control and acceleration of damage areas epithelialization;
- Easy transportation and storage;
- Individualization of therapy, taking into account patients' intercurrent diseases and possible appliance for treating different age groups without the involvement of medical personnel at home, office, field, and battlefield conditions;
- Economical affordability.[1,14]

The whole process of obtaining a biopolymer film can be conveniently divided into several stages.

Stage I: Choosing active ingredients are a very important step in the development of any medication. Correct and rational selection of necessary ingredients determines the pharmacological properties of the medication. Therefore, the choice of the active substance and its amount should meet the goal, that is, therapeutic indications and the effects that it should have. For example, in addition to reparative and antibacterial properties, films can also have anesthetic, immunomodulating, antihistaminic, astringent, ones, etc.[15-17]

The active substance must be compatible with all components of the polymer film. Thus, it is necessary to study it properly before proceeding directly to the technological process; to determine whether the medication is compatible with film-forming components and excipients. This stage is proved experimentally.

Stage II: Selecting excipients. A polymer film is not only the medicinal substance but also a diverse number of combinations of film-forming substances that fulfill such basic tasks as removing exudate and toxic substances from a wound surface, effective healing of lesions and strong fixation to the damaged area without sticking. This combination should not only be optimal and stable toward active substances but also have the necessary conditions for releasing and absorbing these substances. Thus, the film will fully ensure its therapeutic effect.

As well as choosing active substance, choosing auxiliary substances requires not only theoretical justification but also experimental one. Besides, it is necessary to explain the role of each auxiliary element participating in forming the basis for the future film.[3,18]

When creating a dosage form of a biodegradable film, such film-forming components as sodium carboxymethylcellulose and polyvinyl alcohol are most often used. Polyethylene oxide-400 and glycerol are used as dispersing agents and plasticizers.[19-21] The proposed combination of polymers and glycerin allows obtaining the necessary film qualities – elasticity, adhesiveness, homogeneity, the absence of breakage and microflaws, and good peeling from a substrate. Films are made by drying a solution of polymers.

The variety of active ingredients and excipients combinations has helped to create a wide range of combinations in one dosage form. For example, at the pharmaceutical market, there can be found the wound coating, which is a biologically active biodegradable dressing based on collagen and chitosan with the inclusion of the Furaginum antiseptic and local anesthetic anilocaine.[22-25]

An important factor affecting physical and mechanical properties of dental films (breaking strength, relative elongation, and elasticity) is using plasticizers and their concentration. Glycerin, dibutyl phthalate and polyethylene glycols are most often used as plasticizers.[26-28]

Surface-active materials which can influence the API release time are used as solubilizers, wetting or dispersing agents. Dimethyl sulfoxide, benzalkonium chloride, sodium lauryl sulfate, etc., may be used for this purpose as well.

Technological process

One technology or a combination of several technologies can be used to produce various types of films (dental, vaginal, oral, and eye) one or. The standard technology is pouring on a surface.[1-15] Preparing gelling solution, the first stage of which is the dissolution stage precedes pouring. Depending on the properties of the ingredients, it is possible to dissolve hydrophilic polymers in water separately, heating it, and to dissolve active and auxiliary substances in matching solvents with further combining the formed solutions; or to dissolve auxiliary substances insolvent or a mixture of solvents, and then adding active pharmaceutical ingredients to this solution. After stirring and obtaining a homogeneous viscous system, degassing is performed to remove air bubbles by centrifuging, vacuum suction or leaving it at rest for certain time. After weighing, the amount of solvent evaporated during preparing is added to the film-forming solution, and the next stage is pouring on the chosen surface (glass, plastic, metal, etc.) itself. Drying, depending on the technology chosen and the properties of the substances, is performed at room temperature or heating to 40–60°C, then the film is removed from the supporter and cut into pieces of the required size.[29-31]

The solution can also be applied to the surface with a spray (in the form of spray), which allows to get very thin films, but such technology is difficult to exploit, provided that the viscosity of the disperse system is high and is more often used to produce quick-dissolving oral films.

The modification of the pouring method is pouring the gel. In this case, a solution of a water-soluble film-forming component is prepared. The formed solution is added to a solution of a polymer insoluble in acids (for example, acetate phthalate cellulose or acetate butyrate cellulose) in a solution of sodium hydroxide or ammonia. While applying this method, the ratio of water-soluble polymers and insoluble in acids ones should be 4:1. After that, the necessary amount of plasticizer is added to form the gel mass. The gel is poured into molds or applied on a drying belt by rolling between the drums.[15,26,32,33]

In addition to pouring, extrusion techniques are also used. The method of hot melt extrusion is characterized by the fact that the active and auxiliary substances are blended in a solid state, and then put into an extruder equipped with a heater, and a film is formed from this molten mass. The melt extrusion has a number of advantages over other methods due to reducing the number of process operations, improving the homogeneity of films and absence of water in the process, but it is not suitable for films containing thermolabile material. When applying the cold-extrusion method, films are produced of a mixture of solid ingredients using dies. The films have much lower elasticity than those obtained by the pouring method, therefore, the extrusion methods are more often used for producing fast-dissolving buccal or oral films.[34-36]

Classification of oral film

There are three different subtypes
1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained-release.

Quality control of the films is carried out according to the following parameters: The appearance and size of the film, dissolution time, pH of the aqueous solution, defining the average weight, homogeneity of the mass, dissolution time, mechanical strength, and vapor permeability.[3,15,21,24,32,36]

Application of films in medicine

Polymer films have applications in various fields such as Wound Healing, Dental, Diabetes, and Ophthalmology [Figure 1].

Treating purulent wounds remains one of the most important problems of modern medicine. Nowadays, patients with this pathology account for about 40% of surgical patients. Furthermore, the problem is to restore the lost skin at

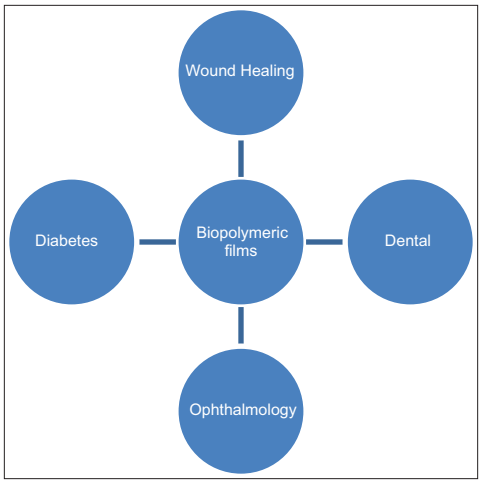

Figure 1: Commercial applications of biopolymeric films

infectious diseases and traumas of various etiologies. A kind of a dosage form for treating patients with skin defects, which are the results of purulent infection of soft tissues, are wound dressings.[2,7,12,13,36] The correct choice of a wound dressing with a certain mechanism of action can significantly improve the effectiveness of the purulent wounds treatment. Nowadays, more than 300 types of wound dressings are used in clinical practice. In practical surgery, the procedure for treating purulent wounds under the bandage remains the main one in clinical practice, since it is most convenient and economically sound. Wound dressings for many centuries have been used to stop bleeding and protect the wound from recontamination. However, recently physicians have found the results of treating wounds with the help of traditional dressings less satisfactory. The disadvantage of many wound dressings have been used is their sticking to a wound. As a result, the regenerating tissues get injured, and dressing itself is painful.

Causes of long non-healing wounds can be: Trophic ulcers, bacterial anaerobic infections, burn injuries - all this often leads to the development of purulent and necrotic processes. The problem of this pathology remains topical and unsolved, and is getting more and more socioeconomically significant. That is why specialists from all over the world are interested in wound dressings based on polymers.

Polymer films can be applied not only in surgery but also in dentistry.[37] The films are compatible with most medications; do not have irritating effect on the oral mucosa. In addition, the polymer base forms a perfect homogeneous mixture with the mucous membranes secrets and cleans the wound surface well. Due to its quick and aimed action onto a pathological are, removing toxic substances and wound exudate, this dosage form is rational to use for complicated forms of periodontitis, stomatitis, and gingivitis.

In the treatment of inflammatory periodontal diseases, traditional dosage forms, such as rinses, pastes, emulsions, aerosols, are most often applied.[38] However, many of them

have a number of complications, which significantly reduces their therapeutic properties. Although the oral cavity, teeth, and gums are isolated zones, continuous moistening with the saliva causes quick washing the medication into the lower parts of the digestive canal, which requires repeated medication administration. In addition, modern methods of treating periodontal inflammatory diseases require the emphasis on local delivery of antimicrobial agents using controlled release systems of active pharmaceutical ingredients.[16,34,35,39] Dental films on a polymeric basis meet such requirements. While applying dental films, the polymeric base is gradually dissolved under the influence of saliva, and there is prolonged release and diffusion of the active pharmaceutical ingredient to the tissue of the mucous membrane of the oral cavity and paradontium.[18] Dental films have advantages over other traditional dental forms: They increase the bioavailability and effectiveness of active pharmaceutical ingredients, protect them from washing off with saliva, and at the same time allow using different therapeutic and physicochemical properties of the substance.

Diabetes mellitus is a fast growing medical problem in affluent societies and a critically attack on the metabolic activity of the patient. In Ukraine, this disorder is increasing in an alarming manner as compared to most of the developing and developed countries. Hence, we need to concentrate on these diseases. Biofilms have been linked to several good phenomenon and several scary diseases.

Nowadays, most of them have using polymer films for ophthalmology. Applications of polymers in ophthalmology include vitreous replacement fluids, contact lenses, intraocular lenses, glaucoma drainage devices, viscoelastic replacements, drug delivery systems, sclera buckles, retinal tacks and adhesives, and ocular endotamponades.[40]

CONCLUSIONS

1. Based on the review, polymer films have been classified, and the requirements for the given dosage form have been defined;
2. Approaches to selecting active and auxiliary ingredients have been considered;
3. The main aspects of the technological process for the preparation of films are described;
4. The ways of rational application of films in medical practice have been highlighted.

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