BIOPOLYMER PACKAGING MATERIALS IN THE PHARMACEUTICAL INDUSTRY

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Abstract: Due to environmental concerns, biopolymer packaging materials are gaining prominence in the pharmaceutical industry. These biopolymers are derived from renewable sources and offer biodegradability, biocompatibility, and non-toxicity, making them ideal for various pharmaceutical applications. In drug delivery, biopolymers are crucial in controlled-release formulations, especially for personalized medicines and biopharmaceutical products. Hydrogels, three-dimensional polymer networks, are key in mimicking living tissues and facilitating stimuli-responsive drug release with minimal toxic effects. The formulation strategies involve diffusion-controlled, degradation-controlled, or environmentally triggered release. Biodegradable systems, for instance polymers like poly(lactic acid) and poly(glycolic acid), contribute to sustainable drug delivery by undergoing controlled degradation. Osmotic delivery systems leverage osmotic pressure for controlled drug release, while stimuli-responsive designs respond to environmental changes. Biopolymer integration in pharmaceutical packaging aligns with eco-friendly practices, addressing challenges posed by traditional petroleum-based materials. This shift signifies a sustainable and innovative approach to pharmaceutical packaging in harmony with environmental preservation.

Keywords: Biopolymer; Biomaterials; Biodegradable polymers; Pharmaceutical forms; Pharmaceutical formulation

1. Introduction

Many food, pharmaceutical, and other products integral to modern life require protection during distribution from manufacturers to consumers and are packaged in different packaging materials depending on their purpose. Various packaging materials are available, including glass, metal, paper and cardboard, wood, polymer mono, multilayer, and composite materials, from which suitable packaging is formed (jars, bottles, boxes, cans, tubes, bags, containers, combo packs, cups, etc. [1,2].

In recent years, due to the critical global environmental deterioration caused by global warming, the establishment of systems with sustainable material use has been accelerated. This is about the perspective of more efficient utilization of limited carbon

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resources and conserving limited energy resources. The Kyoto Protocol and the desire to reduce society's dependence on imported crude oil have directed research efforts toward using biomass as energy and chemicals for consumer goods. Additionally, the price of petroleum raw materials has dramatically increased, leading to a growing consumer interest in using "green" (or renewable) sources as the basis for consumer products [3].

The question of sustainability is being considered through the possibilities of adopting increased use of biopolymers from renewable sources as an alternative to traditional polymers derived from petroleum. Biopolymers now play a significant, albeit relatively minor, role in various industries. This can be linked to sustainability regarding variables such as raw material supply, water and energy use, and waste generation. The growth of production, human resources, and technological development also needs to be viewed through the lens of sustainability. Since most biopolymers are either biodegradable or compostable, it can be argued that biopolymers, primarily fitting into the "cradle to cradle" concept, can become the "food" for the next generation of materials [4].

Biopolymers are obtained from starch, sugars, natural fibers, or other organic biodegradable components of various compositions. Biopolymers degrade when soil, compost, or marine sediment are exposed to bacteria. When biodegradable biopolymers are disposed of as waste, utilizing their property of being degradable by soil bacteria, there is a significant reduction in CO_2 emissions compared to conventional incineration. Therefore, attention is being drawn to using biodegradable biopolymers to prevent global warming. Biodegradable biopolymers offer hope in addressing the issues associated with the disposal of conventional polymers [3].

Despite some drawbacks, biodegradable polymers are gaining importance as conventional polymers are non-degradable and depleting fossil fuel resources. While biopolymers face numerous challenges, including reducing production costs, broader availability, improving their thermomechanical and barrier properties, biodegradability rates, availability, and optimizing composting processes, the demand for biopolymers is increasing, and their application areas are constantly expanding. Given the increased demand and expanded use, these challenges are expected to be addressed and overcome, producing biopolymers with desired characteristics and properties [4].

Pharmaceutical packaging is demanding and highly regulated, and it must comply with numerous regulations and approvals from government agencies worldwide. The packaging of medicines changes slowly because safety in the pharmaceutical industry must be ensured. Therefore, extensive research begins when a new material becomes available and is proposed as packaging for a new product. Developing and qualifying a new material often requires parallel development of packaging machinery, sterilization processes, or both, which is hard to justify unless the result significantly improves the product or production [5].

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The adoption of newer polymers, such as bio-derived polylactic acid (PLA), remains a topic for the future. Considering the growing importance of environmental issues, the application of biopolymers, which have advantages and disadvantages, as packaging for pharmaceutical products will be the subject of future research. Also, these materials presented in the context of packaging offer exciting possibilities as resorbable materials. They are materials that can be introduced into the body and then absorbed over time, which can be applied in the production of certain drugs, as well as medical devices used in surgery, orthopedics, and dentistry [5].

Although bipolymers are rarely used in the pharmaceutical industry for packaging, they have significant applications as auxiliary substances for producing various forms of pharmaceutical preparations (tablets, capsules, gels, etc.), where they play different roles. The application of biopolymers has become extremely important with the introduction and implementation of complex therapeutic systems (drug delivery systems), which play a crucial role in the controlled and desired release of drugs in the body [6–27].

2. Application of biopolymers in the pharmaceutical industry

Biopolymers are traditionally used in pharmaceutical products as excipients, such as binding agents, fillers, thickeners, and disintegrants. A review of the Pharmaceutical Handbook of Excipients [14] reveals many biopolymers listed for pharmaceutical use. Biopolymers are employed in most pharmaceutical dosage forms, including oral use, ocular use, nasal sprays, topical formulations (gels and ointments), lung delivery forms, and even parenteral delivery. Traditional drug forms are the subject of much research to improve drug stability and efficacy, reduce costs, increase patient adherence to prescribed therapy, and enhance therapeutic performance. The wide range of biopolymers, available as diverse compounds with various properties and of natural origin with the possibility of easy production, makes them popular in pharmaceutical research. In addition to numerous applications in traditional dosage forms, biopolymers have recently been used for the controlled delivery of biological substances such as proteins, peptides, and vaccines [17].

Pharmaceutical dosage forms based on the release rate of the active substance, the rate of achievement, and the duration of action after administration can be broadly classified into:

- Conventional pharmaceutical forms,
- Modified release pharmaceutical forms.

Modern unconventional drug dosage forms represent a highly heterogeneous group of complex systems and special carriers of active substances, including:

- Drug delivery systems (DDS),

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• Drug carriers, Drug carrier systems [7].

Carriers for biological therapeutic substances (active substances obtained by modern biotechnological methods/biopharmaceutical drugs) range from well-known natural excipients to purposefully designed synthetic excipients with "enhanced" protection and targeting capabilities. However, natural and semi-synthetic excipients still prevail. The widespread use of biopolymers results from a good understanding of their properties (long-term service experience) and good physiological tolerance. Another reason for their use is that new synthetic substances require extensive and expensive safety testing before human use. This complicates their timely evaluation, except for using in vitro and animal models [7].

2.1. Application of biopolymers in the formulation of conventional pharmaceutical forms

Conventional pharmaceutical dosage forms are formulations with immediate release of the active substance. They are characterized by frequent use, relatively rapid achievement of therapeutic drug concentrations in the blood, and fluctuations in drug concentrations (upon repeated drug administration). According to the definition in the European Pharmacopoeia (Ph. Eur.), these formulations represent preparations that exhibit the release of the active substance(s) that is not modified by the composition of the formulation and/or the manufacturing process [7]. Conventional dosage forms can be defined as those in which the control of drug release into surrounding biological fluids is limited [18].

The use of biopolymers in the formulation of conventional pharmaceutical dosage forms has garnered significant attention in recent years due to their diverse properties and potential benefits. Biopolymers derived from natural sources exhibit biocompatibility, biodegradability, and often enhanced safety profiles compared to their synthetic counterparts. In pharmaceutical formulations, biopolymers find application in various dosage forms such as tablets, capsules, and coatings, contributing to the overall quality, performance, and acceptability of patients of these formulations.

Biopolymers are crucial in tablet formulation, serving as fillers, binders, and disintegrants. Natural polymers like starch, alginate, and cellulose derivatives are used as fillers to increase the tablet's mass. They also act as binders, improving the cohesion of tablet particles during compression. Some biopolymers exhibit disintegration properties, promoting rapid tablet breakdown for efficient drug release [19].

Biopolymers are also extensively used in tablet coatings to enhance aesthetics, mask unpleasant tastes, and facilitate swallowing. Film coating, a widely accepted method, employs natural polymers such as modified starch. These coatings improve the visual appeal of tablets, contribute to stability, and modify drug release characteristics [18,22].

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Biopolymers find application in capsule formulation, where they can serve as coating materials or be used for encapsulating drugs. This allows controlled drug release and may improve overall bioavailability [28].

In injectable formulations, biopolymers can be used to improve drug stability, control drug release, and enhance the rheological properties of the formulation [29].

2.2. Application of biopolymers in the formulation of pharmaceutical dosage forms with modified release

There are several strategies for formulating pharmaceutical dosage forms with modified release. Instead of developing new drugs or bioactive compounds (which can be expensive), many pharmaceutical companies now use modified/continuous delivery technologies to improve existing therapeutic agents by controlling the rate at which they enter the bloodstream, thereby reducing and avoiding under- or over-dosing. The release of biologically active agents from the delivery system can be either diffusion-controlled (diffusion of the drug through a rate-controlled barrier/matrix), degradation-controlled (chemical or physical disruption of the matrix leading to the release of the bioactive agent), or environment-triggered (changes in pH, ionic strength, or pressure adapted to release the bioactive substance) [17].

Biopolymers usually have a more complex chemical structure and are biocompatible compared to synthetic polymers. They can be easily adapted to the development of matrices for controlled release. The key drawback of biopolymers is their susceptibility to microbiological contamination. Generally, these polymers are biocompatible, non-toxic, and biodegradable. Hydrogels are a key means of modifying, controlling, or maintaining delivery. They consist of three-dimensional, insoluble (bio)polymeric networks capable of absorbing large amounts of water or biological fluids and can be designed for stimulus-response release. Compared to other synthetic biomaterials, hydrogels mimic living tissues quite well due to their similar chemical building blocks, exhibiting reduced toxicity and inflammatory effects. The hydrophilic nature of biopolymers provides water-binding properties. At the same time, other physical or chemical cross-links form a three-dimensional network that helps retain structural integrity when in an aqueous environment [17].

Parameters used to characterize the suitability of hydrogels for a specific application include:

- The volume fraction of the polymer in the swollen state measures the amount of liquid absorbed and retained by the hydrogel.
- Average molecular weight of the polymer chain between two adjacent cross-linking points: provides a measure of the degree of cross-linking of the polymer.

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- Size of openings/pores between polymer chains: measures the space between biopolymer chains available for diffusion.

The preparation of hydrogels usually involves cross-linking functional groups (e.g., hydroxyl, amine, amide, ether, carboxylate, and sulfonate) along the polymer chain to increase the rigidity of the network. The design of the hydrogel microstructure depends partly on the targeted route of administration and the properties of the incorporated compound. Hydrogels are often formed using specific molds to obtain the appropriate size and conformation for maximum effective delivery, depending on the routes of administration, e.g., orally (spherical beads, cylinders, and discs), in implants (in the form of discs and cylindrical preparations) [17].

The drug release mechanism can be chemical or physical but always involves some form of diffusion. Diffusion-controlled release systems can be divided into three categories: reservoir systems, matrix systems, and other diffusion-controlled release systems [17,18].

In reservoir systems, the drug's core is separated from biological fluids by a water-soluble polymer coating or layer, depending on the geometry of the drug delivery system. Polymers commonly used as coatings include ethyl cellulose, poly(ethylene-vinyl acetate), silicones, and acrylic copolymers. Figure 1 schematically represents the design and operation of the reservoir system for controlled drug release [18]. In hydrogels, the type of reservoir system medicinal compounds (solid or liquid) are incorporated into a reservoir within a microporous or non-porous polymeric network [17]. The release of the drug from these systems occurs through a series of steps. Initially, it involves the drug's distribution in the coating's polymer layer. The drug diffuses from the inner to the outer side of the coating layer due to the difference in concentration gradient. At this stage, it is distributed to the surrounding biological environment. Reservoir systems for controlled release can be produced in various shapes, including conventional tablets, laminated films, and other defined forms (e.g., hemispheres, cylinders, sticks). There are numerous methods by which systems, e.g., pellets, spheres, and tablets, can be coated with an insoluble polymer coating using conventional spray film techniques. All reservoir systems for drug delivery share a typical design, i.e., the drug core is located within a polymeric barrier. The composition of the polymeric membrane is made following the drug's physicochemical properties, especially the therapeutic agent's ability to diffuse through the polymer coating at an appropriate rate, the chosen method of production, and the proposed method of application to the patient [18].

In matrix systems for controlled release (release) of drugs, the drug is homogeneously dispersed, either at the molecular level or as solid particles, in a polymeric medium. Compared to reservoir systems, the production of matrix systems for the controlled release of drugs is more advanced and economical and can be performed using a variety of approaches [17,18].

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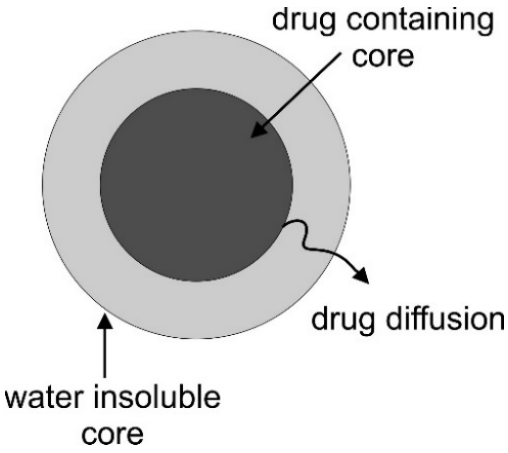

Figure 1. Schematic representation of the design and operation of the tank system for controlled release [18].

Examples of matrix systems for modified release include:

- Mixing polymers with drug particles, followed by direct compression into tablets - this is called the direct compression method and is used to produce matrix systems with controlled release. Cellulose derivatives, such as hydroxypropyl methylcellulose and sodium carboxymethylcellulose, can be applied to produce these controlled-release pharmaceutical forms because these two polymers offer advantages for planning the required drug release rate. Other possible approaches include the compression of cellulose derivatives with an acrylic derivative (Eudragit E100) and a combination of poly(ethylene oxide) with hydroxypropyl methylcellulose in the formation of multilayer tablets.
- Dissolving the drug and polymer in an appropriate solvent with subsequent removal of the solvent in some cases, the drug is dissolved/dispersed in the polymer solution, then poured into a proper mold before removing the solvent. Also, matrix systems containing drugs can be used as drug-release coatings for medical devices. In addition to preparing matrix systems using film/coating methods, methods such as spray-drying micro-particle production and solvent evaporation from emulsion can be applied.
- Incorporation of the drug into the polymer by polymerizing the drug-monomer mixture or swelling a hydrogel in the drug solution – incorporation of drugs into these systems is carried out either by polymerization or cross-linking of monomers in the presence of dissolved or dispersed drugs or by immersing a cross-linked hydrogel in the drug solution to allow drug absorption into the polymer matrix.
- Polymer hardening in a plastic mass in the presence of dissolved/dispersed drug [18].

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Examples of systems that exhibit controlled release through swelling are physically or chemically cross-linked gels. In terms of controlled drug release, chemically cross-linked hydrogels are used to provide controlled drug release from a medical device, while physically controlled swelling hydrogels can be quickly produced by direct compression of the drug with a hydrophilic polymer, such as hydroxypropyl methylcellulose [23]. These swelling-controlled delivery systems are initially dry and swell after absorbing the solvent medium. Swelling increases the water content within the formulation with an increase in drug dissolution, allowing drug diffusion from the swollen network to the external environment [17].

Biodegradable systems are those in which the drug is embedded in a matrix composed of a biodegradable polymer, i.e., the polymer undergoes controlled degradation within the biological environment. As a result, the polymeric matrix's molecular weight decreases after ingestion due to the hydrolysis of cross-links or hydrolysis of the main polymer chain. Thus, the previously insoluble polymeric matrix becomes soluble in biological fluids, facilitating elimination. There are several examples of biodegradable polymers for which applications with controlled release have been tested. They include poly(lactic acid), poly(glycolic acid), and their copolymers, poly(ε-caprolactone), etc. [18].

In osmotic controlled delivery systems, the difference between the osmotic pressure within the formulation and the surrounding biological fluids is utilized as the driving force for drug release. The first (elementary) osmotic-controlled drug delivery systems consisted of two basic parts: a tablet core (containing the drug and an osmotic pressure modifier when needed) and a semipermeable membrane (Figure 2). The general mechanism of drug release from these systems involves the diffusion of gastrointestinal fluid through the semipermeable membrane at a controlled rate and the dissolution of the drug. If an osmotic pressure modifier is present, a saturated solution of the drug in the tablet core will be formed. As the number of molecules in the solution increases, the osmotic pressure in the tablet core increases. The outer coating (semipermeable membrane) is rigid, reducing the osmotic pressure within the tablet. A saturated drug solution is released from the tablet core through laser-drilled holes [18].

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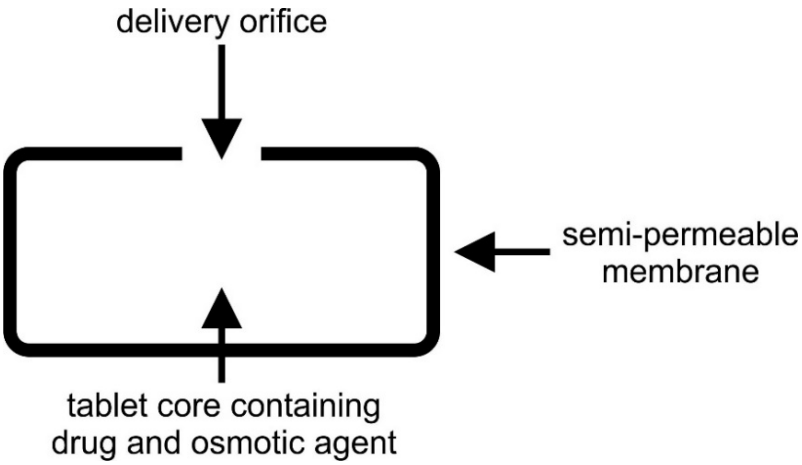

Figure 2. Design of a basic osmotically controlled drug delivery system [18].

The possibility of designing dosage forms to release the drug after application to the appropriate stimulus (stimulation) is another aspect of great interest in drug delivery [18]. An ideal delivery system should respond to physiological demands, sense changes, and change its release profile accordingly. The symptoms of most diseases follow a cyclic pattern and require drug delivery to reflect these cycles. If the drug has unwanted effects, it is released when it is not needed, representing an additional burden on the body's metabolic system. Delivery patterns should be optimized to have a self-regulatory mechanism. Hydrogels can exhibit significant changes in swelling behavior, network structure, permeability, or mechanical strength in response to stimuli (stimuli) such as temperature and pH [17]. Polymers that respond to stimuli are often referred to as "smart" polymers, and after exposure to external signals (temperature, pH, etc.), these systems change their structural and physical properties [18].

3. Conclusions

In recent years, sustainable materials have gained increasing importance due to the critical global environmental deterioration. Sustainability issues are being considered through the possibilities of increased use of biopolymers from renewable sources as an alternative to traditional polymers derived from petroleum. The rise in ecological awareness has led to the need for the creation of biodegradable/degradable packaging materials. The application of biopolymers in pharmaceutical products is significant, ranging from the traditional use of biopolymers as excipients (binding agents, fillers, thickeners, and disintegrants) in most pharmaceutical forms to recent benefits for the controlled delivery of biological substances (proteins, peptides, and vaccines). An essential application of

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biopolymers is seen in delivering personalized medicines, primarily for biopharmaceutical products and tissue engineering. The diverse and characteristic properties of biopolymers, along with their non-toxicity, biodegradability, and biocompatibility, recommend them as ideal carriers for modified and targeted drug delivery, which will contribute significantly to the progress in medical practice in the future, not only in controlled release of therapeutic compounds but also in the development of regenerative medicine.

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