JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/42036

SHORT REVIEW

Role of Natural Polymers in Novel Drug Delivery Systems

Nirmal Shah*, Ghanshyam Parmar, Dipti Gohil, Rajesh Maheshwari, Chintan Aundhia and Sunil Kardani

Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Vadodara - 391760, Gujarat, India; nimspharma@gmail.com

Abstract

Natural polymers have gained significant attention in the field of drug delivery due to their inherent biocompatibility, biodegradability, and low toxicity. This review article aims to provide a comprehensive overview of the diverse roles that natural polymers play in the development of novel drug delivery systems. Beginning with a classification of natural polymers based on their origin (plant, animal, microbial), we explore their unique characteristics and advantages over synthetic counterparts. The review discusses the pivotal role of natural polymers in formulating various drug delivery systems, including sustained/controlled release formulations, targeted delivery platforms, mucoadhesive systems, and nanotechnology-based approaches. Techniques such as emulsification, ionotropic gelation, coacervation, and electrospinning for natural polymer-based drug delivery are elucidated, highlighting their versatility and applicability across different administration routes. Furthermore, we delve into the diverse applications of natural polymers in drug delivery, encompassing oral, transdermal, ocular, injectable, nasal, buccal, and vaginal delivery routes. Recent advances and innovations in combining natural polymers with synthetic counterparts, incorporating stimuli-responsive properties, and personalized medicine approaches are also explored. Despite the numerous advantages offered by natural polymers, challenges such as variability in polymer properties, standardization issues, scale-up challenges, and regulatory considerations are discussed. The review concludes with future perspectives, highlighting emerging trends and opportunities for further research and development in the field of natural polymer-based drug delivery systems. Overall, this review provides valuable insights into the pivotal role of natural polymers in advancing drug delivery technology, paving the way for safer, more efficient, and patient-friendly therapeutic interventions.

Keywords: Efficient Therapy, Improved Bioavailability, Natural Polymers, Novel Drug Delivery

1. Introduction

Drug delivery systems play a crucial role in ensuring the effective and targeted delivery of therapeutic agents to the site of action within the body. They encompass a wide range of technologies designed to enhance the pharmacokinetic and pharmacodynamic properties of drugs while minimizing adverse reactions and improving patient conformity. The arena of novel drug delivery has evolved significantly over the years, driven by advances in materials science, nanotechnology, biotechnology, and pharmaceutical sciences.

Delivery system optimizes drug release kinetics, ensuring optimal amount of drug at the target site over a prolonged period to enhance therapeutic efficacy[1]. Controlled release formulations reduce systemic toxicity by minimizing peak plasma concentrations and maintaining therapeutic levels within the therapeutic window. Novel drug delivery systems offer convenient dosing regimens, reducing the frequency of administration and improving patient adherence to treatment protocols. Targeted drug delivery systems allow for site-specific accumulation of drugs, minimizing off-target effects and maximizing therapeutic outcomes[2].

*Author for correspondence

Article Received on: 13.03.2024 Revised on: 12.08.2024 Accepted on: 14.08.2024

Natural polymers play a critical part in the drug delivery due to their unique properties and biocompatibility. Few important aspects of natural polymers are mentioned herewith. Natural polymers, such as proteins, polysaccharides, and nucleic acids, are inherently biocompatible and are less likely to cause adverse reactions or immune responses when introduced into the body. This makes them ideal candidates for drug delivery systems as they reduce the risk of toxicity[3].

Many natural polymers are biodegradable such as alginates, proteins, polysaccharides and gelatin[4,5], meaning they can be broken down into smaller, non-toxic components by biological processes in the body. This characteristic is advantageous for the delivery system because it facilitates sustained delivery of medication over time and eliminates the need for removal or extraction procedures after treatment. Natural polymers offer a wide range of chemical functionalities and structural diversity, allowing for the design of drug delivery systems tailored to specific therapeutic needs. For example, proteins like albumin can be modified to carry and deliver various types of drugs, while polysaccharides like chitosan can form nanoparticles for the targeted delivery[4].

Natural polymers such as chitosan, guar gum, karaya gum, tamarind seeds and aloe vera mucilage[5] can be planned to control the release rate and distribution of drugs within the body. By modifying their chemical structure or incorporating specific drug-binding motifs, researchers can design carriers that may release therapeutics in a sustained or triggered manner, improving efficacy and minimizing side effects[5]. Thahera PD has showed efficient dissolution profile of gastro retentive formulation using guar gum[6]. Bhatt P *et al.*, has found that the specific alteration of natural polymer-based system can be attained by the implementation of adjustable plasma therapy, that may develop exceptional drug delivery systems which exhibit improved efficiency, bioavailability and tailored administration[7].

Natural polymers such as pectin and inulin[8] can be functionalized to target the defined sites within the body. By attaching ligands or antibodies to the polymer backbone, carriers can selectively deliver the drugs to diseased sites while sparing healthy tissues, thereby improving efficiency and reducing non target effects. Ravi T has found that *in vitro* studies of novel colon targeted drug delivery system using natural polymers such as pectin and inulin showed partial the drug release profile in stomach and small intestinal environment while maximum amount of drug was released in the colonic environment[8].

Unlike synthetic polymers, natural polymers such as chitosan, alginate. cellulose, xantham gum and hyaluronic acid[9] are often recognized as native components by the body's immune system. This reduces the likelihood of immune responses or rejection reactions, making natural polymers attractive for long-term drug delivery applications.

Natural polymers are sourced from renewable biological materials, such as plants, animals, or microorganisms, making them more environmentally sustainable than synthetic polymers derived from fossil fuels. This aspect is increasingly important in the improvement of eco-friendly systems[10]. Some of naturally occurring polymers such as zeoturb, lignin and carrageenan are widely used for environmental sustainability[11].

Overall, the importance of natural polymers in medicament delivery lies in their capability to provide safe, effective, and targeted delivery of therapeutics while minimizing adverse effects on the body and the environment. Their biocompatibility, biodegradability, versatility, and targeting capabilities make them valuable tools for advancing drug delivery technologies and improving patient outcomes[12].

The objectives of a review on role of natural polymers in novel delivery systems are to provide a comprehensive understanding of the current landscape, challenges, and future prospects in harnessing natural polymers to enhance delivery efficiency, therapeutic efficacy, and patient outcomes.

2. Types of Natural Polymers

Natural polymers can be classified based on their origin into several categories. Here's a classification based on the biological sources from which they are derived[13]:

2.1 Plant-based Polymers

2.1.1 Cellulose

Derived from plant cell walls, cellulose is the linear polysaccharide composed of glucose elements. It is widely used in pharmaceutical delivery systems, particularly as matrix material for the controlled release formulations.

2.1.2 Starch

Obtained from grains, roots, and tubers, starch is a carbohydrate polymer consisting of glucose units. It is employed as a biocompatible excipient and matrix material in pharmaceutical formulations.

2.1.3 Pectin

Found in the cell walls of fruits and vegetables, pectin is a heteropolysaccharide composed of galacturonic acid units. It is utilized in drug delivery systems for its gelling, mucoadhesive, and controlled-release properties.

2.2 Animal-based Polymers

2.2.1 Gelatin

Derived from collagen, gelatin is a protein polymer obtained from animal connective tissues. It is employed in drug delivery systems as a matrix material, coating agent, or carrier due to its biocompatibility and gel-forming properties.

2.2.2 Chitosan

Obtained from chitin, which is found in the exoskeletons of crustaceans and cell walls of fungi, chitosan is a polysaccharide composed of glucosamine and N-acetylglucosamine units. It is utilized in drug delivery for its mucoadhesive, bio adhesive, and permeation-enhancing properties.

2.3 Microbial-based Polymers

2.3.1 Hyaluronic Acid

Produced by bacterial fermentation or extracted from animal tissues, hyaluronic acid is a linear polysaccharide composed of repeating disaccharide units. It is used for its biocompatibility, viscoelasticity, and targeting capabilities.

2.3.2 Xanthan Gum

Produced by fermentation of carbohydrates by the bacterium *Xanthomonas campestris*, xanthan gum is a polysaccharide made up of glucuronic acid, mannose and glucose units. It is employed in drug delivery as a viscosity modifier, stabilizer, and mucoadhesive agent.

2.4 Marine-based Polymers

2.4.1 Alginate

Obtained from brown seaweeds, alginate is a linear polysaccharide composed of guluronic acid and mannuronic acid units. It is utilized in drug delivery systems for its gel-forming, mucoadhesive, and controlled-release properties.

2.4.2 Carrageenan

Extracted from red seaweeds, carrageenan is a linear sulphated polysaccharide composed of galactose units. It is employed in drug delivery as a gelling agent, stabilizer, and mucoadhesive agent.

These classifications represent some of the major categories of natural polymers based on their biological origin. Each type of natural polymer offers unique properties that can be harnessed for various drug delivery applications, ranging from oral formulations to injectable depots and implantable devices[14]. The pictorial form of various types of natural polymers is depicted in Figure 1.

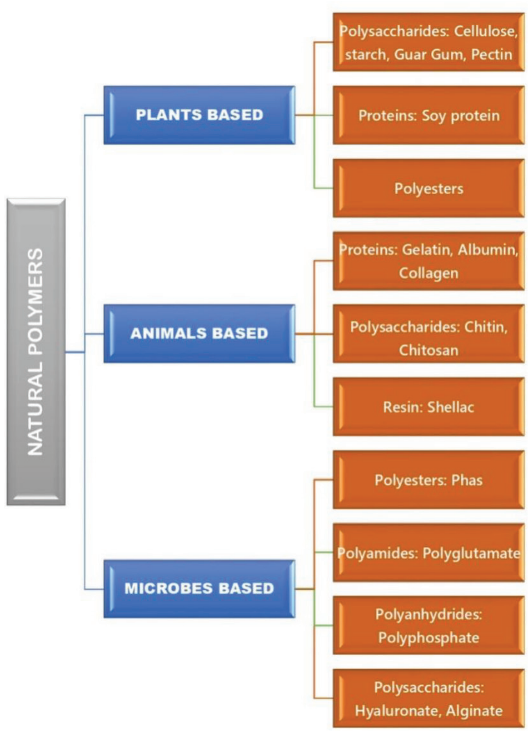

Figure 1. Various types of natural polymers.

3. Natural Polymers Used in Drug Delivery Systems

3.1 Cellulose

Cellulose is extensively used in pharmaceutical dosage forms as a viscosity modifier, binding agent and sustained release material. It is an organic polysaccharide comprising of a linear chain of several hundred to over ten thousand β (1→4) linked D-glucose.

3.2 Chitosan

Chitosan is a polysaccharide derived from chitin, a natural polymer found in the exoskeletons of crustaceans and cell walls of fungi. It is widely used in drug delivery systems due to its biocompatibility, mucoadhesive properties, and permeation-enhancing effects. Examples of chitosan-based drug delivery systems include nanoparticles, microparticles, hydrogels, and films for oral, nasal, ocular, and transdermal delivery[15].

3.3 Alginate

Alginate forms hydrogels and useful for encapsulating the cells, proteins, and drugs in controlled-release formulations. Alginate-based drug delivery systems include microspheres, beads, scaffolds, and dressings used for oral, injectable, and topical delivery applications.

3.4 Hyaluronic Acid

Hyaluronic Acid (HA) is utilized in drug delivery systems for its biocompatibility, viscoelasticity, and targeting capabilities. HA-based formulations include hydrogels, nanoparticles, liposomes, and injectable depots used for intra-articular, ocular, and dermatological delivery of therapeutics.

3.5 Gelatin

Gelatin is a protein found in animal connective tissues. It is widely used in dosage forms as coating material, capsule shell, and matrix material for controlled-release drug delivery systems. Gelatin-based drug delivery systems include microspheres, nanoparticles, films, and hydrogels for oral, parenteral, and topical applications.

3.6 Albumin

Serum albumin is a major protein component of blood plasma. It is utilized in drug delivery systems as a carrier for hydrophobic drugs, imaging agents, and therapeutic proteins. Albumin-based formulations include nanoparticles, microspheres, and conjugates used for targeted drug delivery, imaging, and albumin-based therapies[16].

These examples represent a subset of commonly used natural polymers in drug delivery systems. Each polymer offers unique properties that can be tailored to specific formulation requirements, routes of administration, and therapeutic applications.

4. Advantages of Natural Polymers in Drug Delivery

Natural polymers offer several advantages in drug delivery applications in comparison with synthetic polymers[17,18].

- They are biocompatible, biodegradable with low immunogenicity.
- They can be easily modified or functionalized to enhance their properties, such as encapsulation efficiency, stability, and targeting capabilities.
- Their production often has lower environmental impact and carbon footprint.
- Natural polymers are often easier to process and formulate into drug delivery systems compared to synthetic polymers. They can be fabricated using relatively simple and cost-effective techniques, such as solvent casting, emulsification, or electrospinning, making them attractive for large-scale production[19].
- Natural polymers are generally perceived as safer and more acceptable by regulatory agencies for use in biomedical applications, including drug delivery.

5. Role of Natural Polymers in Formulation Development

Natural polymers show a critical role in the improvement of pharmaceutical formulations, especially in drug delivery systems. Their unique properties contribute to the design, stability, efficacy, and safety of various dosage forms[20-22].

5.1 Matrix Formation

Natural polymers can form matrices that encapsulate drugs and control their release rates. For example, hydrophilic polymers like cellulose derivatives (e.g., Hydroxypropyl Methylcellulose, (HPMC)) and alginate can be used to form gel matrices for sustained-release tablets or capsules.

5.2 Stabilization

Natural polymers can stabilize drugs by preventing degradation, aggregation, or chemical interactions. For instance, proteins like albumin can be used to stabilize protein drugs during formulation and storage, protecting them from denaturation or enzymatic degradation.

5.3 Enhanced Solubility

Hydrophilic natural polymers such as cyclodextrins and hyaluronic acid can enhance the solubility and bioavailability of poorly water-soluble drugs by forming inclusion complexes or increasing dissolution rates.

5.4 Bio-adhesion and Muco-adhesion

Natural polymers with adhesive properties, such as chitosan and pectin, can improve the residence time and adhesion of dosage forms at mucosal surfaces, enhancing drug absorption and bioavailability.

5.5 Targeted Delivery

Natural polymers can be functionalized or modified to target specific tissues, cells, or receptors. For example, ligand-conjugated polysaccharides like hyaluronic acid can target receptors overexpressed on cancer cells, facilitating targeted drug delivery and reducing systemic toxicity.

5.6 Sustained and Controlled Release

Natural polymers can control the release of drugs over time, allowing for sustained or controlled release profiles. This may be achieved through various means such as degradation, diffusion and erosion[23].

5.6 Protection of Encapsulated Agents

Natural polymers can protect encapsulated drugs, genes, or cells from harsh environmental situations such as pH, temperature and enzymatic degradation. This is particularly important for sensitive biomolecules, such as peptides, nucleic acids, and live cells, in gene therapy or cell therapy applications[24].

5.7 Biocompatibility and Safety

Natural polymers are generally biocompatible and less likely to cause adverse reactions or immune responses compared to synthetic polymers. Their use in formulation development enhances the safety profile of dosage forms, reducing the risk of toxicity or side effects.

5.8 Regulatory Acceptance

Natural polymers are often perceived as safer and more acceptable by regulatory agencies for use in pharmaceutical formulations. Their natural origin and history of safe use in food and cosmetics contribute to their regulatory acceptance and expedite the approval process for new drug products.

6. Techniques for Natural Polymer-based Drug Delivery

Natural polymer-based drug delivery systems employ various techniques for formulation, characterization, and application[25]. Here are some common techniques used in the development of natural polymer-based drug delivery systems.

6.1 Solvent Evaporation/Emulsification

This technique involves dissolving the natural polymer such as gelatin and albumin and the drug in a suitable organic solvent, followed by emulsification in an aqueous phase to form droplets. The solvent is then evaporated under reduced pressure or by stirring to form solid nanoparticles or microparticles. This method is commonly used for preparing natural polymer-based nanoparticles and microparticles[26].

6.2 Ionic Gelation

Ionic gelation is a method used specifically for polysaccharides like alginate and chitosan. It involves the formation of crosslinked hydrogels or nanoparticles by complexation with divalent cations (e.g., calcium ions) or polyelectrolytes. This technique is often employed for the preparation of hydrogel beads, nanoparticles, and microspheres for controlled drug release[27].

6.3 Self-assembly

Self-assembly techniques involve the spontaneous organization of natural polymers such as polysaccharides, proteins, and peptides into nanostructures, such as micelles, liposomes, and vesicles, in aqueous solution. This technique is used to encapsulate drugs within the hydrophobic core or bilayer of nanostructures, enabling controlled release and targeted delivery of therapeutics[28].

6.4 Coacervation/phase Separation

Coacervation or phase separation is a technique used to form polymer-rich phases in aqueous solutions by adjusting the pH, temperature, or concentration of natural polymers of gelatin, chitosan, pectin, etc. This method is employed for encapsulating drugs within polymer microspheres or microcapsules, allowing for controlled release and protection of sensitive drugs[29].

6.5 Electrospinning

Electrospinning is a technique used to produce nanofibers from natural polymer (collagen, cellulose, keratin and gelatin) solutions or melts. A high voltage is applied to a polymer solution or melt, causing it to form a jet that is stretched into fine fibres as it is deposited onto a collector. Electrospun nanofibers have high surface area-to-volume ratios and can be used for controlled drug release, wound healing, and tissue engineering applications[30].

6.6 Layer-by-layer Assembly

Layer-by-layer assembly involves the sequential deposition of alternating layers of natural polymers and charged molecules onto a substrate or template. This technique is used to fabricate multilayer thin films, capsules, or coatings for drug delivery, surface modification, and tissue engineering applications.

6.7 Spray Drying

Spray drying is a method used to produce dry powder formulations from liquid formulations containing natural polymers (alginate and cellulose) and drugs. The liquid formulation is atomized into fine droplets, which are then dried using hot air or inert gases to form dry powder particles. Spray drying is suitable for preparing inhalable formulations, solid dispersions, and micro encapsulated powders for pulmonary drug delivery[31].

7. Applications of the Natural Polymers in Drug Delivery

Natural polymers find numerous applications in pharmaceutical sowing to their versatile characteristics such as biodegradability and biocompatibility[32]. Few of them are discussed below.

7.1 Oral Drug Delivery

Natural polymers such as alginate, chitosan, and pectin are used in oral dosage forms due to their muco-adhesive properties, which enhance drug absorption and bioavailability in the gastrointestinal tract. These polymers are employed in the formulation of tablets, capsules, microspheres, and nanoparticles for oral administration[33].

7.2 Injectable Drug Delivery

Natural polymers like hyaluronic acid, gelatin, and collagen are utilized in injectable dosage forms for extended-release profile, targeted delivery, and tissue regeneration applications. Injectable hydrogels, microspheres, and nanoparticles formulated with natural polymers enable localized delivery of drugs, growth factors, and cells to specific tissues or organs[34]. Canepa C *et al.*, has prepared for improved oral administration of interferon-α showed promising antiviral activity and animal study comparable to that of commercial IFNα[35].

7.3 Transdermal and Topical Drug Delivery

Natural polymers such as cellulose derivatives, chitosan, and gelatin are employed in transdermal and topical drug delivery systems for enhanced skin penetration, sustained release, and targeted delivery of therapeutics. Hydrogels, patches, films, and nanoparticles formulated with natural polymers enable controlled release of drugs through the skin for systemic or local effects[36]. Stagnoli S *et al.*, has prepared topical alginate-gelatin hydrogel systems for the controlled release of antineoplastic drugs and concluded that it is extremely consistent and robust technique for carrying complex insoluble chemotherapeutical molecules, and it is found less invasive than other alternative approaches in the literature[37].

7.4 Ocular Drug Delivery

Natural polymers like hyaluronic acid, chitosan, and alginate are used in ocular drug delivery systems for prolonged retention, enhanced bioavailability, and reduced irritation. Ophthalmic solutions, inserts, nanoparticles, and hydrogels formulated with natural polymers enable sustained release and targeted delivery of drugs to the various sites of the eye[38]. Kim DJ *et al.,* has observed that the application of hyaluronic acid-based nanocomposite hydrogels enhanced the healing of corneal epithelium and significantly reduced corneal limbal vascularization, opacity and conjunctival fibrosis[39].

7.4 Nasal and Pulmonary Drug Delivery

Natural polymers such as chitosan, alginate, and cyclodextrins are employed in nasal and pulmonary drug delivery systems for improved drug absorption, reduced mucociliary clearance, and targeted delivery to the respiratory tract. Nasal sprays, inhalable powders, nanoparticles, and liposomes formulated with natural polymers enable efficient delivery of drugs to the nasal cavity, lungs, and airways[40]. Athamneh T *et al.*, has found that alginate- hyaluronic acid microspheres are conceivably appropriate as drug carrier for pulmonary delivery due to their low density a high porosity with good in vitro aerodynamic characterstics[41].

7.5 Parenteral Drug Delivery

Natural polymers like albumin, dextran, and silk fibroin are utilized in parenteral dosage forms for stabilization, controlled release and targeting of drugs. Liposomes, micelles, nanoparticles, and hydrogels formulated with natural polymers enable intravenous, intramuscular, and subcutaneous administration of therapeutics with enhanced safety and efficacy. Wang Z *et al*, has developed albumin-based etoposide-loaded nanosuspension for parenteral formulation and found that the optimized formulation played a significant role in targeting a drug to lung with decrease toxicity and adveralbumin-based etoposide as compared to marketed injection of drug[42].

7.6 Gene and Cell Therapy

Polymers such as gelatin, hyaluronic acid and chitosan are employed in gene and cell therapy applications for nucleic acid carriage and tissue engineering. Nanoparticles, scaffolds, and hydrogels formulated with natural polymers enable efficient delivery of genes, sirna, mirna, and cells to target tissues or organs for therapeutic purposes[43]. Liu CW *et al.*, had developed gelatin-based nanocomposites for gene delivery and found enhanced gene delivery in AY-27 cells *in vitro* and to rat urothelium by intravesical instillation *in vivo*[44].

7.7 Diagnostic Imaging

Natural polymers like alginate, chitosan, and dextran are used in diagnostic imaging applications for contrast enhancement, targeting, and drug delivery. Nanoparticles, microbubbles, and liposomes formulated with natural polymers enable imaging agents to accumulate at specific sites within the body, enhancing the visualization and detection of diseases.

These shows importance of natural polymers in dosage forms in improving the safety, efficacy, and patient compliance of pharmaceutical formulations across various routes of administration and therapeutic modalities.

8. Recent Advances and Innovations

8.1 Natural Polymers in Personalized Medicine

The use of natural polymers in personalized medicine holds significant promise for tailoring therapies to individual patients based on their unique genetic makeup, physiological characteristics, and medical history[45]. Here are some keyways in which natural polymers are utilized in personalized medicine:

8.1.1 Patient-specific Systems

Natural polymers can be employed to formulate personalized systems that cater to the definite requirements of the individual patients. By adjusting parameters such as polymer composition, drug loading, and release kinetics, personalized dosage forms can be designed to optimize therapeutic outcomes while minimizing side effects and adverse reactions.

8.1.2 Targeted Therapy

Natural polymers can be functionalized or modified to incorporate targeting ligands or receptors that selectively recognize and bind to diseased cells or tissues. By precisely delivering medicaments to site of the action, targeted drug delivery systems enhance treatment efficacy and reduce systemic toxicity, particularly in personalized cancer therapy where tumour-specific targeting is crucial. Sabra S *et al.*, has reviewed that hydrophobically-modified polysaccharides and proteins are fascinating much consideration as micelle making polymers to entrap poorly soluble anti-cancer drugs and can be exploited for active-targeted drug delivery by conferring specific targeting ligands to the outer micellar hydrophilic surface[46].

8.1.3 Patient-specific Dosage forms

Natural polymers are utilized in the development of patient-specific dosage forms tailored to individual preferences and requirements. For example, 3D printing technologies enable the fabrication of customized tablets, implants, or scaffolds composed of natural polymers that match the patient's anatomy and pharmacokinetic profile, improving drug absorption, bioavailability, and patient compliance[47].

8.1.4 Personalized Diagnostics and Imaging

Natural polymers have importance in personalized diagnostic and imaging agents for disease detection, monitoring, and treatment planning. By conjugating natural polymers with contrast agents, targeting moieties, or diagnostic markers, personalized imaging probes can be engineered to provide real-time information about disease progression, response to therapy, and patient-specific biomarkers. Jaymand M has reviewed that chemically modification of natural polymers may lead to significant development in theranostic nanomedicines that lead to have enhanced therapeutic benefit to the patients[48].

8.1.5 Tissue Engineering and Regenerative Medicine

Natural polymers serve as scaffolds, matrices, and carriers for tissue engineering and regenerative medicine applications aimed at repairing or replacing damaged tissues and organs. By combining natural polymers with patient-derived cells or growth factors, personalized tissue-engineered constructs can be created to promote tissue regeneration, organ repair, and functional restoration[39].

8.1.6 Patient-specific Pharmacogenomics

Natural polymers are utilized in the delivery of pharmacogenomic agents, such as sirna or mirna, to modulate gene expression and tailor drug responses based on individual genetic variations. By incorporating patient-specific genetic information into drug delivery systems, personalized pharmacogenomic therapies can optimize drug efficacy, minimize adverse drug reactions, and improve patient outcomes.

8.1.7 Personalized Nutrition and Nutraceuticals

Natural polymers are utilized in personalized nutrition and nutraceutical formulations tailored to individual dietary requirements, nutritional deficiencies, and health goals. By encapsulating bioactive compounds, vitamins, or micronutrients within natural polymer-based delivery systems, personalized nutraceuticals can optimize nutrient absorption, bioavailability, and metabolic response.

8.2 Incorporation of Stimuli-responsive Properties

Incorporating stimuli-responsive properties into drug delivery systems enhances their efficacy and specificity by enabling precise release of therapeutic agents in the response to specific environmental triggers or external stimuli. Natural polymers offer unique advantages for designing stimuli-responsive drug delivery systems due to their important properties[50,51]. Few examples for stimuli-responsive properties are listed below:

8.2.1 PH-responsive Systems

Natural polymers such as chitosan, alginate, and pectin exhibit pH-responsive behaviour, undergoing structural changes in response to variations in pH. pH-responsive drug delivery systems can be designed to release drugs selectively in acidic or alkaline environments, such as the acidic tumour microenvironment or the alkaline gastrointestinal tract. For example, chitosan-based nanoparticles can be formulated to discharge the drugs in response to the acidic pH of tumour tissues, improving drug accumulation and efficiency with decreased adverse effects[52].

8.2.2 Temperature-responsive Systems

Thermo responsive natural polymers, such as gelatin, exhibit phase changes in response to the variations in temperature, leading to reversible sol-gel transitions. Temperature-responsive dosage forms can be fabricated to release drugs in a temperature-dependent manner, enabling localized drug delivery at elevated temperatures, such as those found in inflamed or infected tissues. For instance, thermosensitive hydrogels composed of gelatin can be injected as a liquid at room temperature and undergo gelation at body temperature, facilitating sustained drug release at the site of administration.

8.2.3 Enzyme-responsive Systems

Natural polymers can be modified or conjugated with enzyme-sensitive moieties that undergo cleavage or degradation in the presence of specific enzymes. Enzyme-responsive drug delivery systems can be engineered to release drugs in response to enzymatic activity associated with certain diseases or physiological processes. For example, hyaluronic acid-based nanoparticles can be modified with enzyme-cleavable linkers that release encapsulated drugs upon exposure to disease-specific enzymes, such as matrix metalloproteinases overexpressed in tumour tissues[53].

8.2.4 Redox-responsive Systems

Natural polymers like dextran and chitosan can be modified with redox-sensitive bonds that undergo reduction or oxidation in response to changes in the cellular redox environment. Redox-responsive systems can be engineered to release drugs selectively in reducing or oxidizing conditions, such as those found in intracellular compartments or diseased tissues. For instance, disulfide bonds can be incorporated into dextran nanoparticles to enable intracellular drug release in the cytoplasm, where high concentrations of reducing agents are present.

8.2.5 Light-responsive Systems

Natural polymers can be functionalized with photo-responsive groups that undergo photochemical reactions or conformational changes upon exposure to specific wavelengths of light. Light-responsive systems can be engineered to release drugs with spatial and temporal control, enabling remote activation of drug release at targeted sites. For example, light-sensitive hydrogels composed of photosensitive polymers like azobenzene can be used to generate drug release in respect to the external light stimuli, allowing for on-demand drug delivery with high precision[54].

By incorporating stimuli-responsive properties into drug delivery systems using natural polymers, it is possible to achieve spatiotemporal control over drug release, improve targeting efficiency, and enhance therapeutic efficacy while minimizing systemic toxicity and off-target effects. These innovative drug delivery platforms hold great promise for advancing personalized medicine and improving patient outcomes transversely an extensive range of diseases and medical conditions.

9. Market Trends

The food, textiles, water treatment, and cosmetics products in the present market contain natural polymers as emulsifiers and as antimicrobial and thickening agents. The product EUDRAGUARD® that is naturally coated pellets contains maize starch which is claimed to have taste masking property. The product Protect™ is an enteric coated tablets containing shellac and sodium alginate and probiotic Pearls™ is coated pellets containing sodium alginate and pectin both are having the property of protecting the drug molecules in the acid environment in the stomach[55].

10. Challenges and Limitations

While natural polymers offer numerous advantages for pharmaceutical drug delivery systems, they also present certain challenges and limitations that need to be addressed. Some of the key challenges and limitations include variability in source and composition, poor mechanical strength and stability, limited drug loading and encapsulation efficiency, fast degradation and clearance, immunogenicity and allergenicity, limited control over properties, regulatory challenges, cost and scalability.

11. Future Perspectives and Conclusion

The future of natural polymer-based drug delivery is bright, with emerging trends and advancements poised to address unmet medical needs, improve patient outcomes, and usher in a new period of personalized and precision medicine. By harnessing the unique properties and capabilities of natural polymers, researchers and practitioners can unlock novel therapeutic strategies and transformative treatment modalities for an extensive range of the diseases and medical conditions.

12. References

1. Mainardes RM, Silva LP. Drug delivery systems: past, present, and future. Current drug Targets. 2004; 5(5):449-55. https://doi.org/10.2174/1389450043345407 PMid:15216911
2. Manish G, Vimukta S. Targeted drug delivery system: a review. Research Journal of Chemical Sciences. 2011; 1(2):135-8.

3. Rajeswari S, Prasanthi T, Sudha N, Swain RP, Panda S, Goka V. Natural polymers: A recent review. World Journal of Pharmacy and Pharmaceutical Sciences. 2017; 6:472-94. https://doi.org/10.20959/wjpps20178-9762
4. Satchanska G, Davidova S, Petrov PD. Natural and synthetic polymers for biomedical and environmental applications. Polymers (Basel). 2024; 16(8):1159. https://doi.org/10.3390/polym16081159 PMid:38675078 PMCid:PMC11055061
5. Sharma D, Dev D, Prasad DN, Hans M. Sustained release drug delivery system with the role of natural polymers: A review. Journal of Drug Delivery and Therapeutics. 2019; 9(3):913-23. https://doi.org/10.22270/jddt.v9i3-s.2859
6. Thahera PD, Ashok M, Latha K, Shailaja T, Nyamathulla S, Uhumwangho MU. Formulation and evaluation of norfloxacin gastro retentive drug delivery systems using natural polymers. International Current Pharmaceutical Journal. 2012; 1(7):155-64. https://doi.org/10.3329/icpj.v1i7.10809
7. Bhatt P, Kumar V, Subramaniyan V, Nagarajan K, Sekar M, Chinni SV, et al. Plasma modification techniques for natural polymer-based drug delivery systems. Pharmaceutics. 2023; 15(8):2066. https://doi.org/10.3390/pharmaceutics15082066 PMid:37631280 PMCid:PMC10459779
8. Ravi V, TMP Kumar, Siddaramaiah. Novel colon targeted drug delivery system using natural polymers. Indian J Pharm Sci. 2008; 70(1):111-3. https://doi.org/10.4103/0250-474X.40346 PMid:20390095 PMCid:PMC2852048
9. Murphy EJ, Fehrenbach GW, Abidin IZ, Buckley C, Montgomery T, Pogue R, *et al.* Polysaccharides-naturally occurring immune modulators. Polymers. 2023; 15(10):2373. https://doi.org/10.3390/polym15102373 PMid:37242947 PMCid:PMC10222865
10. Carmen Chifiriuc M, Mihai Grumezescu A, Grumezescu V, Bezirtzoglou E, Lazar V, Bolocan A. Biomedical applications of natural polymers for drug delivery. Curr Org Chem. 2014; 18(2):152-64. https://doi.org/10.2174/138527281802140129104525
11. Matei E, Predescu AM, Rapa M, **Ţurcanu** AA, Mateş I, Constantin N, *et al*. Natural polymers and their nanocomposites used for environmental applications. Nanomaterials. 2022; 12(10):1707. https://doi.org/10.3390/nano12101707 PMid:35630932 PMCid:PMC9146209
12. Tong X, Pan W, Su T, Zhang M, Dong W, Qi X. Recent advances in natural polymer-based drug delivery systems. React Funct Polym. 2020; 148:104501. https://doi.org/10.1016/j.reactfunctpolym.2020.104501
13. Sun H, Klok HA, Zhong Z. Polymers from nature and for nature. Bio Macromolecules. 2018; 19(6):1697-700. https://doi.org/10.1021/acs.biomac.8b00830 PMid:29886748
14 Olatunji O, Richard O. Processing and characterization of natural polymers. Natural Polymers. 2016; 19-61. https://doi.org/10.1007/978-3-319-26414-1_2 PMCid:PMC5562057
15. Bangar B, Shinde N, Deshmukh S, Kale B. Natural polymers in drug delivery development. Research Journal of Pharmaceutical Dosage Forms and Technology. 2014; 6(1):54-7.
16. Tiwari P, Panthari P, Katare DP, Kharkwal H. Natural polymers in drug delivery. World Journal of Pharmacy and Pharmaceutical Sciences. 2014; 3(9):1395-409.
17. Priya VS, Roy HK, Jyothi N, Prasanthi NL. Polymers in drug delivery technology, types of polymers and applications. Scholars Academic Journal of Pharmacy. 2016; 5:305-8. https://doi.org/10.21276/sajp.2016.5.7.7
18. Kulkarni VS, Butte Kishor D, RathodSudha S. Natural polymers - A comprehensive review. International Journal of Research in Pharmaceutical and Biomedical sciences. 2012; 3(4):1597-613.
19. Anwunobi AP, Emeje MO. Recent applications of natural polymers in nanodrug delivery. J Nano Med Nano Technol. 2011; 4(002):1-6. https://doi.org/10.4172/2157-7439.S4-002
20. Pahwa R, Bhagwan S, Kumar V, Kohli K. Role of natural polymers in the development of floating drug delivery systems. J Pharm Res. 2010; 3(6):1312-8.
21. Das S, Deshmukh R, Jha AK. Role of natural polymers in the development of multiparticulate systems for colon drug targeting. Systematic Reviews in Pharmacy. 2010; 1(1):79-85. https://doi.org/10.4103/0975-8453.59516
22. Kandar CC, Hasnain MS, Nayak AK. Natural polymers as useful pharmaceutical excipients. In Advances and Challenges in Pharmaceutical Technology, Academic Press. 2021. p. 1-44. https://doi.org/10.1016/B978-0-12-820043-8.00012-8
23. Mogoşanu GD, Grumezescu AM. Pharmaceutical natural polymers: structure and chemistry. Handbook of polymers for pharmaceutical technologies: structure and chemistry. 2015;1:477-519. https://doi.org/10.1002/9781119041375.ch16
24. George A, Shah PA, Shrivastav PS. Natural biodegradable polymers-based nano-formulations for drug delivery: A Review. Int J Pharm. 2019; 561:244-64. https://doi.org/10.1016/j.ijpharm.2019.03.011 PMid:30851391
25. Bhatt P, Kumar V, Subramaniyan V, Nagarajan K, Sekar M, Chinni SV, *et al*. Plasma modification techniques for natural polymer-based drug delivery systems. Pharmaceutics. 2023; 15(8):2066. https://doi.org/10.3390/pharmaceutics15082066 PMid:37631280 PMCid:PMC10459779
26. O'Donnell PB, McGinity JW. Preparation of microspheres by the solvent evaporation technique. Adv Drug Deliv Rev. 1997; 28(1):25-42. https://doi.org/10.1016/S0169-409X(97)00049-5 PMid:10837563
27. Luo Y, Wang Q. Recent development of chitosan-based polyelectrolyte complexes with natural polysaccharides for drug delivery. Int J Biol Macromol. 2014; 64:353-67. https://doi.org/10.1016/j.ijbiomac.2013.12.017 PMid:24360899
28. Chen S, Cheng SX, Zhuo RX. Self-assembly strategy for the preparation of polymer-based nanoparticles for drug and gene delivery. Macromol Biosci. 2011; 11(5):576-89. https://doi.org/10.1002/mabi.201000427 PMid:21188686

29. Blocher WC, Perry SL. Complex coacervate-based materials for biomedicine. Wiley Interdisciplinary Reviews: Nanomedicine and Nano biotechnology. 2017; 9(4):1442. https://doi.org/10.1002/wnan.1442 PMid:27813275
30. Han W, Wang L, Li Q, Ma B, He C, Guo X, *et al*. A review: Status and emerging developments on natural polymer-based electro spun fibers. Macromol Rapid Commun. 2022; 43(21):2200456. https://doi.org/10.1002/marc.202200456 PMid:35842914
31. Malamatari M, Charisi A, Malamataris S, Kachrimanis K, Nikolakakis I. Spray drying for the preparation of nanoparticle-based drug formulations as dry powders for inhalation. Processes. 2020; 8(7):788. https://doi.org/10.3390/pr8070788
32. Olatunji O, editor. Natural polymers: industry techniques and applications. Springer; 2015 Dec 24.
33. Garg A, Garg S, Kumar M, Kumar S, Shukla AK, Kaushik SP. Applications of natural polymers in mucoadhesive drug delivery: An overview. Arch Drug Inf. 2018; 3(2):38-42. https://doi.org/10.31024/apj.2018.3.2.1
34. Lin X, Tsao CT, Kyomoto M, Zhang M. Injectable natural polymer hydrogels for treatment of knee osteoarthritis. Adv Healthc Mater. 2022; 11(9):2101479. https://doi.org/10.1002/adhm.202101479 PMid:34535978
35. Canepa C, Imperiale JC, Berini CA, Lewicki M, Sosnik A, Biglione MM. Development of a drug delivery system based on chitosan nanoparticles for oral administration of interferon-α. Biomacromolecules. 2017; 18(10):3302-9. https://doi.org/10.1021/acs.biomac.7b00959 PMid:28837330
36. Sonawane PR, Katti SA. Natural polymers: carriers for transdermal drug delivery system. International Journal of Research in Pharmacy and Chemistry. 2016; 6(3):534-42.
37. Stagnoli S, Garro C, Ertekin O, Heid S, Seyferth S, Soria G, *et al*. Topical systems for the controlled release of antineoplastic drugs: oxidized alginate-gelatin hydrogel/unilamellar vesicles. J Colloid Interface Sci. 2023; 629:1066-80. https://doi.org/10.1016/j.jcis.2022.08.163 PMid:36303362
38. Ali Z, Kumar Sharma P, Warsi MH. An insight of natural polymers in ocular drug delivery systems. Journal of Chronotherapy and Drug Delivery. 2016; 7(1):7-19.
39. Kim DJ, Jung MY, Pak HJ, Park JH, Kim M, Chuck RS, *et al*. Development of a novel hyaluronic acid membrane for the treatment of ocular surface diseases. Scientific reports. 2021; 11(1):2351. https://doi.org/10.1002/jbm.a.34976 PMid:24124098
40 Carter CK, Puig-Sellart M. Nanocarriers made from non-ionic surfactants or natural polymers for pulmonary drug delivery. Current Pharmaceutical Design. 2016; 22(22):3324-31. https://doi.org/10.2174/1381612822666160418121700 PMid:27087597
41. Athamneh T, Amin A, Benke E, Ambrus R, Leopold CS, Gurikov P, *et al*. Alginate and hybrid alginate-hyaluronic acid aerogel microspheres as potential carrier for pulmonary drug delivery. J Supercrit Fluids. 2019; 150:49-55. https://doi.org/10.1016/j.supflu.2019.04.013
42. Wang Z, Li Z, Zhang D, Miao L, Huang G. Development of etoposide-loaded bovine serum albumin nanosuspensions for parenteral delivery. Drug Deliv. 2015; 22(1):79-85. https://doi.org/10.3109/10717544.2013.871600 PMid:24401038
43. Dang JM, Leong KW. Natural polymers for gene delivery and tissue engineering. Adv Drug Deliv Rev. 2006; 58(4):487-99. https://doi.org/10.1016/j.addr.2006.03.001 PMid:16762443
44. Liu CW, Chang LC, Lin KJ, Yu TJ, Tsai CC, Wang HK, *et al.* Preparation and characterization of gelatin-based mucoadhesive nanocomposites as intravesical gene delivery scaffolds. Biomed Res Int. 2014; 2014(1):473823. https://doi.org/10.1016/j.jconrel.2013.09.019 PMid:24096021
45. Koutsopoulos S. Molecular fabrications of smart nano biomaterials and applications in personalized medicine. Adv Drug Deliv Rev. 2012; 64(13):1459-76. https://doi.org/10.1016/j.addr.2012.08.002 PMid:22921596
46. Sabra S, Abdelmoneem M, Abdelwakil M, Mabrouk MT, Anwar D, Mohamed R, *et al*. Self-assembled nanocarriers based on amphiphilic natural polymers for anti-cancer drug delivery applications. Current Pharmaceutical Design. 2017; 23(35):5213-29. https://doi.org/10.2174/1381612823666170526111029 PMid:28552068
47. Khan FA, Narasimhan K, Swathi CS, Mustak S, Mustafa G, Ahmad MZ, *et al*. 3D printing technology in customized drug delivery system: current state of the art, prospective and the challenges. Current Pharmaceutical Design. 2018; 24(42):5049-61. https://doi.org/10.2174/1381612825666190110153742 PMid:30636582
48. Jaymand M. Chemically modified natural polymer-based theranostic nanomedicines: are they the golden gate toward a de novo clinical approach against cancer? ACS Biomater Sci Eng. 2020; 6(1):134-66. https://doi.org/10.1021/acsbiomaterials.9b00802 PMid:33463213
49. Geraili A, Xing M, Mequanint K. Design and fabrication of drug-delivery systems toward adjustable release profiles for personalized treatment. View. 2021; 2(5):20200126. https://doi.org/10.1002/VIW.20200126
50. Oliveira MB, Mano JF. Natural-based and stimuli-responsive polymers for tissue engineering and regenerative medicine. Polymers in Regenerative Medicine. 2014. p. 49-90. https://doi.org/10.1002/9781118356692.ch2 PMCid:PMC3975948
51. Soleimani K, Derakhshankhah H, Jaymand M, Samadian H. Stimuli-responsive natural gums-based drug delivery systems for cancer treatment. Carbo Hydr Polym. 2021; 254:117422. https://doi.org/10.1016/j.carbpol.2020.117422 PMid:33357903
52. Mutalabisin MF, Chatterjee B, Jaffri JM. PH responsive polymers in drug delivery. Res J Pharm Technol. 2018; 11(11):5115-22. https://doi.org/10.5958/0974-360X.2018.00934.4

53. Kuang T, Liu Y, Gong T, Peng X, Hu X, Yu Z. Enzyme-responsive nanoparticles for anticancer drug delivery. Curr Nano Sci. 2016; 12(1):38-46. https://doi.org/10.2174/1573413711666150624170518
54. Xing Y, Zeng B, Yang W. Light responsive hydrogels for controlled drug delivery. Front Bioeng Bio Technol. 2022; 10:1075670. https://doi.org/10.3389/fbioe.2022.1075670 PMid:36588951 PMCid:PMC9800804
55. Barbosa JA, Conway BR, Merchant HA. Going natural: using polymers from nature for gastroresistant applications. British Journal of Pharmacy. 2017; 2(1):14-30. https://doi.org/10.5920/bjpharm.2017.01