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Applications of Natural and Synthetic Polymeric Nanocarriers in Modern Drug Delivery

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ABSTRACT
Nanomedicine has transformed modern therapeutics by enabling precise and efficient drug delivery, with polymer-based nanoparticles emerging as versatile carriers. Natural polymers such as alginate, chitosan, gelatin, pullulan, and gliadin offer biocompatibility, biodegradability, sand low toxicity, making them attractive for pharmaceutical applications. However, their batch variability and unpredictable physicochemical behavior sometimes limit performance. Synthetic polymers, including polylactide (PLA), polylactide-co-glycolide (PLGA), polyanhydrides, poly-ε-caprolactone, and polyalkyl cyanoacrylates, provide superior structural uniformity and tunable degradation profiles, enabling controlled and targeted drug release. Both natural and synthetic polymers have demonstrated success in enhancing solubility, bioavailability, and therapeutic efficacy while minimizing systemic side effects. This review highlights the comparative advantages, limitations, and applications of polymeric nanoparticles in areas such as cancer therapy, ocular delivery, blood-brain barrier penetration, vaccination, and gene therapy. The integration of natural and synthetic polymers holds promise for designing next-generation nanocarriers tailored to complex clinical challenges.

Keyword: Drug delivery, nanoparticles, bioavailability, biodegradability, Natural polymers, Synthetic polymers etc

I. INTRODUCTION

The advancement of nanomedicine has significantly transformed therapeutic strategies and highlighted the need for more advanced drug delivery systems **(Beach et al., 2024)**. With the increasing prevalence of various diseases, the focus has shifted toward achieving more effective and targeted delivery approaches to improve treatment outcomes. Nanocarriers have emerged as versatile platforms capable of enhancing therapeutic efficacy while addressing common limitations in conventional drug delivery. They are known to improve the solubility and bioavailability of poorly soluble drugs, strengthen preventive and pharmacological actions, and minimize unwanted side effects. Common nanocarrier systems include nanospheres, nanocapsules, nanoemulsions, nanoliposomes, and nanoniosomes**(Jain and Thareja, 2019)**.

A wide range of nanoparticles has been explored for drug delivery, including polymer-based, inorganic, and lipid-based systems **(Huang et al., 2011; Ulbrich et al., 2011)**. Among these, polymeric nanoparticles have gained considerable attention in recent decades due to their versatility and functional significance in drug delivery. These nanosystems, fabricated from polymeric building blocks, stand out because their structural composition allows for tailored and complex designs. Key advantages of polymeric nanoparticles include their tunable size, morphology, and surface charge, which make them highly adaptable for diverse biomedical applications **(Beach et al., 2024)**. Typically, they are recognized as colloidal carriers with particle dimensions ranging from 1 to 1000 nm **(Gref et al., 1994)**.

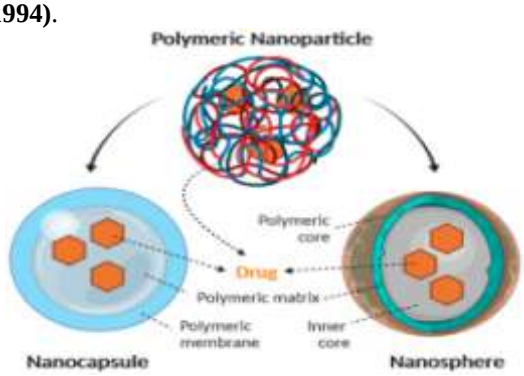

Figure 1. Schematic representation of the structure of nanocapsules and nanospheres (arrow stands for the presence of drug/bioactive within the nanoparticles) (Zielińska et al., 2020)

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Polymeric nanoparticles can be developed using natural, synthetic, or semisynthetic polymers. When prepared from biodegradable and biocompatible materials, these nanocarriers provide significant advantages for achieving controlled and targeted drug delivery **(Gref et al., 1994; Zielińska et al., 2020)**.

Types of polymeric nanoparticles:

Polymer matrices employed as drug carriers can be derived from both natural and synthetic sources **(Geszke-Moritz et al., 2024)**. Natural polymers are often preferred due to their lower toxicity compared to synthetic ones, as they are inherently biocompatible, biodegradable, safe, stable, cost-effective, and relatively easy to process **(Sabra et al., 2019)**. Common examples of naturally occurring biodegradable and biocompatible polymers used in nanoparticle formulation include cellulose, gelatin, pullulan, chitosan, alginate, and gliadin. However, nanoparticles prepared from natural polymers may demonstrate variable in vivo performance since their chemical composition and, consequently, their physicochemical properties can differ significantly **(Chakravarthi et al., 2007)**. Moreover, natural polymers may occasionally induce mild immunogenic responses.

On the other hand, synthetic polymers can be engineered with precise chemical compositions, enabling greater control over their physical properties such as solubility, permeability, and degradation rate. This tunability allows them to be specifically designed for controlled dissolution, targeted delivery, and predictable erosion and biodegradation behaviors. Notable examples of synthetic biodegradable polymers used for nanoparticle fabrication include polylactide (PLA), poly(lactide-co-glycolide) (PLGA), polyanhydrides, poly-ε-caprolactone, and polyphosphazene**(Chakravarthi et al., 2007)**.

Comparison between the natural and synthetic polymers' parameters. Optimized according to reference (Shrivastava, 2018)

Natural Polymers	Synthetic Polymers
In use for millions of years	First produced 125 years ago
Similar or nonidentical repeating units	Identical repeating unit
Properties are naturally controlled	Properties are engineered
Usually biodegradable	Some are biodegradable
The backbone structure is carbon, oxygen, and nitrogen	The backbone is mostly carbon
Environmentally friendly	Some are friendly, and some are toxic to the environment
Limited recyclability	Most of them are capable of being recycled multiple times

Natural Biodegradable Polymers Used to Prepare Nanoparticles

Alginates

Alginate is a linear, unbranched polysaccharide composed of randomly arranged sequences of guluronic and mannuronic acid residues **(Tønnesen and Karlsen, 2002)**. In aqueous environments, sodium ions present in alginate salts can be replaced by divalent cations, such as calcium, leading to the formation of water-insoluble gels **(Rajaonarivony et al., 1993)**. Owing to the mild conditions involved in their processing, alginates serve as excellent carriers for a variety of therapeutic agents, including oligonucleotides **(Ferreiro et al., 2002)**, peptides and proteins **(Gombotz and Wee, 2012)**, as well as water-soluble drugs or those sensitive to organic solvents. They are nonimmunogenic, biocompatible, and available across a broad range of molecular weights, often defined by their intrinsic viscosity.

Alginate nanoparticles are typically produced by dripping an aqueous sodium alginate solution through a fine needle into a solution containing cationic cross-linkers such as calcium ions, chitosan, or poly-L-lysine. These cations interact with guluronic and mannuronic residues, resulting in the formation of a characteristic "egg-box" structure that provides the basis of the gel matrix. Once administered, drug release occurs when the matrix undergoes redissolution due to the exchange of divalent ions with monovalent ones—particularly sodium ions in physiological fluids. A drawback of this mechanism is the possibility of a rapid release of therapeutic agents due to this ion exchange process. For example, alginate

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nanoparticles have been successfully employed to sustain antibacterial drug concentrations in the liver, lungs, and spleen following pulmonary delivery of isoniazid, rifampicin, and pyrazinamide **(Zahoor et al., 2005)**. To extend release profiles, these nanoparticles may be coated with cationic polymers such as poly-L-lysine or chitosan, though the alginate-to-polymer ratio plays a crucial role in determining drug release kinetics and particle characteristics **(De and Robinson, 2003)**.

Chitosan

Chitosan is a naturally occurring polymer produced through the deacetylation of chitin, a structural component of crab shells. Structurally, it is a cationic polysaccharide made up of linear β(1,4)-linked D-glucosamine units. Several methods for formulating chitosan nanoparticles and their applications in drug delivery have been widely reported **(Agnihotri et al., 2004)**. Drugs can be incorporated into chitosan nanoparticles through mechanisms such as chemical cross-linking, ionic cross-linking, or ionic complexation**(Prabaharan and Mano, 2004)**.

Gelatin

Gelatin is a biodegradable natural protein obtained via acid- or base-catalyzed hydrolysis of collagen. It consists of heterogeneous single- and multi-stranded polypeptides enriched with glycine, proline, and hydroxyproline residues, and undergoes enzymatic degradation in vivo to yield amino acids. Gelatin nanoparticles are commonly prepared using a two-step desolvation technique **(Coester et al., 2000)**. In this coacervation process, a water-miscible nonsolvent or another soluble polymer is introduced into a heated aqueous gelatin solution (above ~40 °C). The resulting concentrated gelatin droplets are stabilized and hardened through chemical cross-linking, typically with glutaraldehyde. Alternatively, nanoparticles can be synthesized using emulsion techniques, such as o/w or w/o/w emulsions. Gelatin-based nanoparticles have been employed to deliver drugs like paclitaxel, methotrexate, and doxorubicin, as well as genetic materials including DNA and oligonucleotides. PEGylation of gelatin nanoparticles prolongs their circulation in the bloodstream and improves cellular uptake via endocytosis **(Kaul and Amiji, 2004)**, while surface modification with antibodies allows selective targeting of lymphocytes **(Balthasar et al., 2005)**.

Pullulan

Pullulan is a water-soluble, linear glucan structurally related to dextran and cellulose, consisting of repeating units of three α-1,4-linked glucose residues joined by α-1,6 linkages at the terminal glucose **(Wolf et al., 2003)**. Produced through the fermentation of Aureobasidiumpullulans, pullulan can be chemically modified to introduce hydrophobicity (e.g., via acetylation), promoting self-assembly into nanoparticles with hydrophobic cores capable of entrapping lipophilic drugs. Pullulan nanoparticles can be synthesized by dialysis of an organic solution against water or through reverse micellar techniques, where a drug–polymer aqueous solution is introduced into a reverse micellar system of Aerosol OT in n-hexane. Stabilization is generally achieved by cross-linking with glutaraldehyde**(Gupta and Gupta, 2004)**. These systems have been investigated for the delivery of cytotoxic drugs, genetic materials, and in pH-sensitive formulations.

Gliadin

Gliadin, a glycoprotein derived from gluten-rich sources such as wheat flour, is slightly hydrophobic yet polar, enabling it to encapsulate bioactive molecules of diverse polarity. Gliadin nanoparticles are typically prepared via desolvation, exploiting their poor solubility in water. In this method, nanoparticles are formed when an ethanolicgliadin solution is added to water **(Umamaheshwari and Jain, 2003)**. These nanoparticles have been explored for the delivery of compounds like trans-retinoic acid, α-tocopherol, and vitamin E. Furthermore, surface conjugation with lectins has enabled site-specific targeting of the colon, offering therapeutic potential in the treatment of Helicobacter pylori infections **(Umamaheshwari and Jain, 2003)**.

Synthetic Biodegradable PolymersUsed to Prepare Nanoparticles

Polylactide and Polylactide-co-Glycolide

Polylactic acid (PLA) is a hydrophobic polymer that can be used either in its pure form or copolymerized with polyglycolic acid (PGA) to generate poly(lactide-co-glycolide) (PLGA) with different monomeric ratios, thereby offering a wide range of physicochemical properties. Both PLA and PLGA are FDA-approved polymers extensively applied in drug delivery systems, including nanoparticle formulations. These polymers undergo degradation primarily through random bulk hydrolysis, a process accelerated in

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acidic environments. Numerous preparation methods for PLA- and PLGA-based nanoparticles, along with their physicochemical characteristics, biological fate, applications, and targeting capabilities, have been well documented in the literature **(Bala et al., 2004)**.

Polyanhydrides

Polyanhydrides are a class of biodegradable polymers characterized by a hydrophobic backbone linked with hydrolytically unstable anhydride bonds. They are generally synthesized through ring-opening polymerization and undergo degradation predominantly via surface hydrolysis **(Kumar, 2002)**. Their primary applications have been in the development of films and microspheres designed for localized, sustained release of therapeutic agents, including proteins and drugs.

Poly-ϵ-Caprolactones

Nanoparticles formulated from poly-ε-caprolactone (PCL) have been widely studied, and various preparation techniques such as emulsion polymerization, solvent displacement, dialysis, and interfacial polymer deposition have been reported **(Sinha et al., 2004)**. PCL is a semicrystalline polymer known for its chemical stability, low glass transition temperature, and slow degradation rate, which make it highly suitable for long-term and sustained drug delivery. These nanoparticles have been successfully applied as carriers for different therapeutic agents, including tamoxifen, retinoic acid, and griseofulvin.

Polyalkyl-Cyanoacrylates

Polyalkyl-cyanoacrylate nanoparticles are most commonly produced using the emulsion-evaporation technique. Beyond enabling sustained release, these nanoparticles have shown potential in overcoming multidrug resistance at both cellular and subcellular levels **(Vauthier et al., 2003)**. Their utility in targeted drug delivery has also been demonstrated through surface modification, such as the conjugation of polysaccharides to enhance specificity toward target cells **(Chauvierre et al., 2003)**.

Roles of polymer in drug delivery system:

Polymers play a critical role in drug delivery systems by enhancing the effectiveness, safety, and targeting of therapeutic agents. Their unique properties allow for controlled and sustained release of drugs, improving bioavailability, reducing side effects, and increasing patient compliance **(Ranade, 1990; Srivastava et al., 2015).** The several key roles of polymers in drug delivery discussed as following:

- **Immediate release dosage forms Tablets:** Polymers including polyvinyl -pyrrolidine (PVP) and hydroxypropysl methylcellulose (HPMC) used as binders in formation of granules and improve flow property of tablets **(Pandey et al., 2024).**
- **Capsules:** Polymers used as excipient to increases the bulk weight in capsules. Mostly Gelatin is used as a shell material for hard and soft capsules.
- **Control release drug:** Polymers are used to release the drug in a controlled manner.
- **Enhance bioavailability:** Polymer can improve the BA of drug **(Pandey et al., 2024).**

Application of polymer based nano-particles in biomedical field

1. Corticoids release

Corticosteroids are potent anti-inflammatory agents widely used in the management of posterior segment ocular disorders, including uveitis. They have also been reported to enhance wound healing and may play a role in reducing fibrosis, such as in proliferative vitreoretinopathy and subretinal neovascularization. However, systemic administration of corticosteroids is often associated with significant side effects, making topical delivery the preferred option. Despite this, topical application allows only a limited fraction of the drug to penetrate into the posterior segment. Intravitreal injections can achieve higher therapeutic concentrations, but they usually need to be repeated frequently, causing considerable patient discomfort **(Young et al., 2001; Hainsworth et al., 1996)**. Additionally, this invasive procedure carries risks such as vitreous hemorrhage, retinal detachment, and potential local toxicity. To overcome these limitations, drug-releasing implants have been developed as an alternative to maintain sustained intraocular drug levels **(Young et al., 2001)**. Nonetheless, this approach also has drawbacks, including the need for a large surgical incision for implantation **(Jaffe et al., 2000)**, difficulty in removal, and the possibility of implant migration, which may damage the epithelium **(Tan et al., 1999)**.

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2. Anticancer therapies

In cancer therapy, one of the major challenges is the limited tumor response to treatment, largely due to the nonspecific bioavailability of conventional anticancer drugs. Nanoparticle-based delivery systems offer a promising strategy to enhance drug accumulation at the tumor site. In most cases, this targeted accumulation is facilitated by the **enhanced permeation and retention (EPR) effect**, which allows nanoparticles to preferentially accumulate in tumor tissues. For instance, **Hapca et al. (2009)** developed PLA-based nanoparticles functionalized with monoclonal antibodies, providing high specificity for the treatment of ovarian cancer and lymphomas.

A recent application of nanoparticle carriers is the controlled delivery of heme oxygenase-1 (HO-1) inhibitors **(Iyer et al., 2007)**. HO-1 is an enzyme responsible for the oxidative degradation of heme, involving cleavage of the porphyrin ring to generate biliverdin, carbon monoxide, and free iron. Biliverdin is subsequently converted into bilirubin by biliverdinreductase, where bilirubin serves as a potent antioxidant. While excessive bilirubin levels in the bloodstream may cause neurotoxic effects, in normal physiological concentrations it protects cells against oxidative stress **(Milbury et al., 2006; Shapiro, 2003)**. Interestingly, tumor cells can exploit HO-1 to shield themselves from oxidative damage, with particularly high HO-1 expression observed in renal and prostate cancers. These findings support the hypothesis that HO-1 inhibition could sensitize tumors to oxidative processes, thereby enhancing the efficacy of commonly used chemotherapeutic agents such as cisplatin, anthracyclines, and camptothecin.

3. Blood-brain barrier

The blood–brain barrier (BBB) represents a highly selective physiological boundary between the bloodstream and the central nervous system (CNS). Its primary function is to maintain homeostasis by permitting the exchange of essential ions and nutrients while protecting the brain and spinal cord from chemical and microbial threats. However, this protective role comes with a major drawback: the BBB restricts the entry of most therapeutic agents, making CNS drug delivery particularly challenging. The impermeability of the BBB arises from the presence of tightly packed endothelial cells connected by zonulaoccludens junctions, which effectively block the passage of foreign molecules, including drugs.

Overcoming this limitation has become a significant focus of research. One promising strategy involves encapsulating drugs within nanoparticles. Due to their nanoscale size, these carriers can traverse the vascular endothelium of the BBB, enabling therapeutic agents to reach target sites within the CNS. Several studies have demonstrated encouraging results using drug-loaded nanoparticles for the treatment of brain tumors **(Schroeder et al., 1998; Rousseau et al., 1997)**.

4. Vaccines and gene therapy

Nanoparticles play a crucial role in the field of gene delivery, as they provide effective protection of genetic material against degradation caused by unfavorable factors such as pH, bile, or proteolytic enzymes. However, challenges remain regarding the structural stability of nanoparticle–gene complexes during both formulation and administration. One strategy to overcome this issue is the reversible binding of genes to the surface of nanoparticles or nanocapsules, ensuring gene release at the target site. To enhance biocompatibility, the use of surfactants is generally avoided. For example, **Castadello et al. (2006)** developed a surfactant-free system in which nanoparticles with a poly(methyl methacrylate) (PMMA) core were coated with a polyethylene glycol (PEG) shell containing positively charged groups. In this configuration, PEG provides steric stability, biocompatibility, and biodegradability, while the cationic groups enable DNA binding. Such complexes significantly reduce the risk of physical desorption, making them stable, non-toxic, and suitable for oral administration.

Gene therapy using nanoparticle-based systems holds strong potential in the treatment of neurodegenerative disorders, particularly Parkinson's disease. For instance, controlled delivery of genes encoding **glial cell line-derived neurotrophic factor (GDNF)** has been shown to halt disease progression and sustain dopamine levels despite neuronal loss. Similarly, nanoparticle-mediated delivery of genes related to tyrosine hydroxylase has demonstrated promising outcomes in experimental models **(Suk et al., 2006; Wu et al., 2004)**.

5. Diagnostic

Sun et al., 2006 presented the modality to obtain copper chlorophyllabeled nanoparticles.

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These nanoparticles can be directly traced in vivo by analytical electron microscopy (AEM). Nanoparticles covered with Polisorbate T-80 have been detected in the brain, what proves the existence of endocytosis and/or transcytosis at some extent. Therefore this type of nanoparticles can be used in the functional exploration of the brain**(Houchin-Ray et al., 2007)**.

II. FUTURE PROSPECTS

The future of polymer-based nanoparticles lies in the development of multifunctional and patient-specific delivery systems that can overcome the limitations of current therapies. Hybrid systems that combine natural and synthetic polymers are expected to play a central role, as they can merge the biocompatibility and safety of natural materials with the tunable degradation and mechanical strength of synthetic polymers. Another promising direction is the design of stimuli-responsive polymers capable of releasing drugs in response to environmental triggers such as pH, temperature, enzymes, or redox gradients, thereby ensuring site-specific and controlled delivery. Personalized nanomedicine, supported by advances in polymer chemistry and computational modeling, may allow the formulation of customized nanocarriers tailored to the genetic and physiological profiles of individual patients. At the same time, the integration of diagnostic and therapeutic functions into a single polymeric platform is paving the way for theranostic applications, where disease detection and treatment occur simultaneously. Despite these opportunities, challenges remain in large-scale production, reproducibility, regulatory approval, and ensuring the long-term safety of polymeric nanoparticles. Future research must also focus on eco-friendly and sustainable polymer designs to reduce environmental impact. Collectively, these advancements hold the potential to accelerate the clinical translation of polymer-based nanoparticles, making them an indispensable tool in next-generation precision medicine.

III. CONCLUSION

Polymeric nanoparticles derived from both natural and synthetic sources represent a cornerstone of modern drug delivery systems. Natural polymers excel in safety and biocompatibility, while synthetic polymers offer controlled degradation and reproducible physicochemical properties. Their complementary strengths highlight the potential of hybrid systems to overcome current limitations. With continued advances in polymer chemistry, nanofabrication, and biomedical engineering, polymer-based nanoparticles are expected to revolutionize targeted drug delivery, improve patient compliance, and expand therapeutic options across multiple disease domains. However, future success will depend on addressing challenges related to large-scale manufacturing, regulatory approval, and long-term safety. Ultimately, the rational design of polymeric nanocarriers can bridge the gap between laboratory innovation and clinical application, contributing significantly to precision medicine.

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