Biodegradable Nanoparticles for Sustainable Drug Delivery

Kashfia Haque [1*], Muhit Rana [2], Md Shamsuddin Sultan Khan [3], Tufael [4]

Abstract

This comprehensive review examines the role of biodegradable nanoparticles in advancing sustainable drug delivery systems. It begins by addressing the environmental and health concerns associated with traditional drug delivery methods, highlighting the need for eco-friendly alternatives. The review provides an in-depth analysis of the properties of biodegradable nanoparticles, emphasizing their biocompatibility, versatility, and tunable characteristics, which make them ideal candidates for drug delivery applications. Various synthesis methods for biodegradable nanoparticles, including emulsification, nanoprecipitation, solvent evaporation, and self-assembly techniques, are discussed, along with their advantages and applications. Moreover, the review explores different types of biodegradable nanoparticles, such as polymer-based nanoparticles, lipid-based nanoparticles, and other biodegradable nanoparticle systems, elucidating their unique properties and applications in drug delivery. Additionally, it delves into the mechanisms of drug loading into biodegradable nanoparticles and drug release from these nanoparticles, outlining encapsulation, surface adsorption, and conjugation methods, as well as diffusion, degradation, and swelling-controlled release mechanisms. Overall, this review provides valuable insights into the design and development of biodegradable nanoparticles for sustainable drug delivery, highlighting their potential to revolutionize healthcare technologies while minimizing environmental impact.

Keywords: Nanoparticles, Sustainable Drug Delivery Systems, Biodegradable Nanoparticles, Synthesis Methods, Future Directions.

Significance | Biodegradable nanoparticles are used for sustainable drug delivery, minimizing environmental impact, enhancing patient care, and fostering cost savings in healthcare.

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Introduction

Nanoparticles, characterized by their nanometer-scale dimensions, exhibit unique physicochemical properties that distinguish them as versatile carriers in drug delivery applications (Jong, D. S. 2008). Their small size-to-surface area ratio facilitates efficient drug encapsulation and delivery to target sites within the body, overcoming challenges associated with conventional drug formulations. Through tailored surface modifications, nanoparticles can be functionalized with ligands or antibodies to achieve site-specific targeting, thereby enhancing therapeutic efficacy while minimizing systemic toxicity. (Hans, M., & Lowman, A. M. 2002).

Incorporating sustainability principles into drug delivery systems is imperative to mitigate the environmental impact and ensure long-term viability. Biodegradable nanoparticles, fabricated from biocompatible polymers or lipid-based materials, offer a promising solution by virtue of their ability to undergo degradation into non-toxic byproducts. This environmentally friendly characteristic reduces ecological footprint and addresses concerns regarding the accumulation of non-biodegradable materials in the environment (Leroux, J. et al, 1996). Moreover, the utilization of eco-friendly

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synthesis methods and renewable resources further enhances the sustainability profile of nanoparticle-based drug delivery systems.

Beyond environmental considerations, sustainable drug delivery systems contribute to efficient resource utilization and cost-effectiveness in healthcare (Pitt, C. G et al, 1979). By enabling precise control over drug release kinetics, nanoparticles facilitate the optimization of therapeutic dosing regimens, minimizing the overall drug dosage required for therapeutic efficacy. This not only conserves resources but also alleviates economic burdens associated with healthcare expenditures, fostering accessibility to advanced therapeutic interventions (Jong, D. S. 2008).

In this review, we will delve into the synthesis methods and characterization techniques employed in fabricating biodegradable nanoparticles for drug delivery purposes. Additionally, the types of biodegradable materials utilized, their physicochemical properties, and their implications for drug encapsulation and release kinetics will be explored. Furthermore, the potential applications of biodegradable nanoparticles in targeted drug delivery, sustained release formulations, and combination therapy approaches will be elucidated, shedding light on their translational potential in clinical settings. Finally, considerations regarding biocompatibility, safety profiles, regulatory considerations, and future directions in the field will be discussed to provide a comprehensive overview of this rapidly evolving area of research and development in pharmaceutical sciences.

*2.*Sustainable Drug Delivery Systems

The field of drug delivery is constantly evolving, aiming to improve therapeutic efficacy and patient compliance. However, conventional drug delivery methods often raise concerns about their environmental impact. Traditional drug delivery systems rely heavily on single-use plastics and other non-biodegradable materials (Allen, T. M., & Cullis, P. R. 2004). These materials contribute significantly to medical waste, placing a burden on landfills and potentially leaking harmful chemicals into the environment.

Specific problems associated with traditional use in drug delivery

Traditional drug delivery methods, such as pills, capsules, injections, and topical creams, have served as the mainstay of treatment for centuries. However, they come with several inherent limitations:

2.1. Plastic Packaging and Devices: Blister packs, syringes, inhalers, and other drug delivery devices are often made from plastics. These plastics are not easily recyclable and generate significant plastic waste, contributing to pollution (Autian, J., & Guess, W. L. 1973). The widespread use of plastic packaging and devices in drug delivery poses a significant threat to the environment. These materials, while often convenient and effective in protecting and delivering medications, contribute to a cascade of environmental issues throughout their lifecycle (Nampoothiri et al, 2010).

Plastic materials have been extensively utilized in various aspects of drug delivery due to their versatility, durability, and ease of fabrication. However, their widespread use has raised concerns regarding environmental pollution and potential adverse effects on human health (Autian, J., & Guess, W. L. 1973). One specific problem associated with plastic use in drug delivery is the generation of non-biodegradable waste. Many plastics, such as polyethylene, polypropylene, and polystyrene, persist in the environment for hundreds to thousands of years, contributing to the accumulation of plastic debris in ecosystems worldwide (Geyer et al., 2017).

Furthermore, the manufacturing and disposal of plastic-based drug delivery systems often involve the use of hazardous chemicals and generate harmful emissions. For instance, the production of plastic nanoparticles may require the use of organic solvents, some of which are volatile organic compounds (VOCs) or pose risks to human health and the environment (Abdel-Kader et al., 2020). Improper disposal of plastic-based drug delivery devices can lead to leaching of toxic additives or degradation products into soil and water, potentially contaminating ecosystems and posing risks to wildlife and human populations (Wright et al., 2020).

Another significant concern is the potential for plastic-based drug delivery systems to interact with drugs or biological fluids, leading to adverse effects on drug stability, efficacy, or safety. Plastic materials may leach additives or impurities into drug formulations, altering their chemical composition or physical properties. Additionally, the presence of plasticizers, stabilizers, or other additives in plastic-based drug delivery systems may raise regulatory concerns related to product safety and compatibility with biological systems (Bartlett et al., 2015).

Moreover, the reliance on petroleum-based plastics in drug delivery contributes to carbon emissions and exacerbates dependence on finite fossil fuel resources. The production of plastic materials from fossil fuels is energy-intensive and generates greenhouse gas emissions, contributing to climate change and environmental degradation (Geyer et al., 2017). As concerns about climate change and resource depletion intensify, there is a growing imperative to develop sustainable alternatives to plastic-based drug delivery systems that minimize environmental impact while maintaining therapeutic efficacy and safety.

2.2. Hydrofluorocarbons (HFCs): Hydrofluorocarbons (HFCs) have been utilized as propellants in inhalation drug delivery systems due to their low boiling points and lack of ozone-depleting potential. However, their use in drug delivery poses specific problems related to environmental impact and potential health risks. One significant concern is the contribution of HFCs to climate change as potent greenhouse gasses. While HFCs do not

deplete the ozone layer like their predecessors, chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs), they possess high global warming potentials (GWPs) and can persist in the atmosphere for many years, exacerbating the greenhouse effect and contributing to climate change (Montzka et al., 2018).

Additionally, the production, use, and disposal of HFC-containing drug delivery devices can lead to environmental contamination and pose risks to ecosystems and human health. HFCs are volatile organic compounds (VOCs) that can undergo atmospheric reactions to form secondary pollutants, such as tropospheric ozone and fine particulate matter, which contribute to air pollution and adverse respiratory effects (Kurokawa et al., 2020). Moreover, accidental releases or improper disposal of HFC-containing inhalers or nebulizers can result in direct environmental emissions, further exacerbating their environmental footprint.

Another concern is the potential for HFCs to interact with pharmaceutical formulations and affect drug stability, efficacy, or safety. Inhalation drug delivery systems typically contain a combination of active pharmaceutical ingredients (APIs) and propellant gases, including HFCs, which facilitate drug dispersion and aerosolization. However, the presence of HFCs in drug formulations may lead to chemical interactions or degradation pathways that compromise drug stability or alter therapeutic performance (McDonald et al., 2016). Furthermore, there is limited understanding of the long-term health effects associated with chronic exposure to HFC-containing inhalation products, necessitating further research to assess their safety profiles and potential risks to vulnerable populations.

In response to these challenges, efforts are underway to develop alternative propellants and delivery systems that minimize reliance on HFCs and mitigate their environmental and health impacts. Green propellants, such as hydrofluoroolefins (HFOs) or compressed gasses like carbon dioxide (CO2) or nitrogen (N2), are being explored as environmentally friendly alternatives to HFCs in inhalation drug delivery systems (Tucker et al., 2019). Additionally, advancements in dry powder inhalers (DPIs) and soft mist inhalers (SMIs) offer propellant-free alternatives that reduce environmental emissions and eliminate concerns associated with propellant stability or compatibility with pharmaceutical formulations.

2.3. Manufacturing Processes: The production of conventional drug delivery systems can be energy-intensive and generate air and water pollution. Manufacturing processes play a critical role in drug delivery, influencing the quality, safety, and efficacy of pharmaceutical products. However, specific problems associated with manufacturing processes in drug delivery can arise, ranging from technical challenges to regulatory compliance issues. One significant concern is the potential for variability and inconsistency in product quality due to variations in manufacturing conditions or equipment performance. Variability in critical process parameters, such as mixing speed, temperature, or humidity, can impact the physicochemical properties of drug formulations, leading to variations in drug release kinetics, bioavailability, or stability (Yu, 2015).

Furthermore, the complexity and scale of manufacturing processes in drug delivery can pose challenges in achieving reproducibility and scalability. Many drug delivery systems, such as nanoparticles, liposomes, or microspheres, require specialized manufacturing techniques, including emulsification, spray drying, or solvent evaporation, which may be difficult to scale up for commercial production while maintaining product consistency and quality (Feng et al., 2016). Moreover, the use of novel materials or excipients in drug delivery formulations may introduce additional complexity or regulatory considerations, necessitating thorough process validation and documentation to ensure compliance with regulatory requirements (Cleland et al., 2014).

Another specific problem associated with manufacturing processes in drug delivery is the potential for contamination or impurities that can compromise product safety and patient health. Contaminants may arise from raw materials, equipment surfaces, or environmental sources, leading to product recalls, quality control issues, or adverse reactions in patients (Bhatia et al., 2018). Additionally, the use of solvent-based manufacturing processes in drug delivery, such as solvent casting or spray coating, may introduce residual solvents or degradation byproducts into the final product, raising concerns about toxicity or regulatory compliance (Almeida et al., 2016).

As an alternative, pharmaceutical manufacturers are increasingly adopting advanced manufacturing technologies and quality assurance strategies to improve process control, reduce variability, and ensure product quality and safety. Process analytical technology (PAT) approaches, such as real-time monitoring of critical process parameters and quality attributes, enable continuous process optimization and real-time release testing, enhancing manufacturing efficiency and product quality (Rathore et al., 2018). Additionally, the implementation of quality by design (QbD) principles in drug product development emphasizes a systematic and science-based approach to process design, control, and optimization, facilitating robust and reproducible manufacturing processes (Yu, 2015).

The Need for Sustainable Alternatives

Developing sustainable drug delivery systems is crucial for several reasons as reviewed by Lam, S. S., Xia, C., & Sonne, C. (2022):

Reduced Environmental Footprint: Sustainable systems aim to minimize waste generation, utilize biodegradable materials, and reduce energy consumption during manufacturing. This helps lessen the environmental impact of the healthcare sector.

Improved Patient Care: Sustainable systems can offer extended shelf lives for medications, reducing medication waste and improving access to essential drugs in resource-limited settings.

Cost Savings: Sustainable practices can lead to cost savings in healthcare by reducing reliance on non-biodegradable materials and minimizing waste disposal costs.

Now researchers are exploring various avenues to develop sustainable drug delivery systems. In response to the environmental, economic, and societal challenges associated with traditional manufacturing processes and materials in drug delivery, there is a pressing need for the development and adoption of sustainable alternatives. This imperative reflects the pharmaceutical industry's recognition of the importance of sustainability in delivering safe, effective, and affordable healthcare solutions (Agrahari, V., & Hiremath, P. 2017).

One driving force behind the push for sustainable alternatives in drug delivery is the urgent need to reduce environmental impact. Traditional manufacturing processes often rely on non-renewable resources, generate significant waste, and contribute to pollution and greenhouse gas emissions (Huang, Y et al, 2015). Transitioning to sustainable manufacturing methods and eco-friendly materials presents an opportunity to minimize the industry's ecological footprint, conserve natural resources, and mitigate environmental degradation.

Moreover, the adoption of sustainable alternatives aligns with broader efforts to address climate change and promote environmental stewardship. Sustainable manufacturing practices, such as green chemistry principles and solvent-free technologies, offer opportunities to reduce energy consumption, minimize chemical waste, and lower carbon emissions (Sheldon, R. A. 2012). Similarly, the use of renewable materials, biodegradable polymers, and natural excipients can contribute to the development of environmentally friendly drug delivery systems that are biocompatible, non-toxic, and eco-friendly (Sheldon, R. A. 2014).

Furthermore, sustainable alternatives in drug delivery have the potential to enhance product safety, efficacy, and patient outcomes. By prioritizing biodegradable materials and green manufacturing practices, pharmaceutical companies can minimize the risk of contamination, impurities, or adverse effects associated with traditional manufacturing processes (Sheldon, R. A. 2014). Sustainable drug delivery systems may also offer improved drug stability, controlled release profiles, and targeted delivery mechanisms, leading to optimized therapeutic outcomes and enhanced patient compliance.

In addition to environmental and health benefits, the adoption of sustainable alternatives can yield economic advantages for pharmaceutical companies and healthcare systems. Sustainable manufacturing processes may reduce production costs, enhance operational efficiency, and improve resource utilization, leading to long-term cost savings and competitive advantages in the marketplace. Furthermore, sustainable drug delivery systems may contribute to the development of innovative therapies, personalized medicine approaches, and novel treatment modalities that address unmet medical needs and improve patient care (Kaur, G et al., 2018).

3. Biodegradable Nanoparticles

Biodegradable nanoparticles are nano-sized particles composed of materials that can be broken down by biological processes into smaller components that are metabolized or eliminated from the body. Biodegradable nanoparticles offer a versatile platform for drug delivery, characterized by their unique properties and potential for sustainable applications in medicine. In this chapter, we will explore the key characteristics of biodegradable materials suitable for nanoparticle synthesis and discuss how these properties contribute to sustainable drug delivery solutions. Here we discussed the characteristics of biodegradable materials for nanoparticle synthesis:

3.1. Biocompatibility: Biodegradable materials used in nanoparticle synthesis should exhibit high biocompatibility, ensuring compatibility with biological systems and minimizing the risk of adverse reactions or toxicity. Polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and chitosan are commonly employed due to their biocompatible nature and regulatory approval for biomedical applications (Danhier et al., 2012).

3.2. Degradability: Biodegradable nanoparticles are designed to undergo degradation in physiological conditions, leading to the breakdown of the carrier material into non-toxic byproducts that can be metabolized or excreted from the body. This property is crucial for minimizing long-term accumulation of nanoparticles in tissues and reducing potential side effects associated with their persistence (Mura et al., 2013).

3.3. Tunable Properties: Biodegradable materials offer flexibility in tailoring the physicochemical properties of nanoparticles, including size, shape, surface charge, and degradation kinetics. These tunable properties enable customization of nanoparticle formulations to achieve desired drug release profiles, target-specific delivery, and enhanced therapeutic efficacy (Alexis et al., 2008).

3.4. Composition: Biodegradable nanoparticles primarily consist of biocompatible polymers or lipid-based materials. Commonly utilized polymers include poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), poly(caprolactone) (PCL), and chitosan. Lipid-based nanoparticles encompass liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) (Tran et al., 2019).

3.5. Synthesis Methods: Synthesis techniques for biodegradable nanoparticles encompass emulsification, nanoprecipitation, solvent evaporation, and self-assembly methods. These methods offer

precise control over nanoparticle size, shape, surface properties, and drug loading capacity, critical for tailored drug delivery (Tran et al., 2019).

3.6. Drug Encapsulation: Biodegradable nanoparticles effectively encapsulate various therapeutic agents, including small molecules, proteins, nucleic acids, and peptides. Encapsulation protects drugs from degradation, enhances solubility, prolonged circulation time, and enables targeted delivery to specific tissues or cells (Tran et al., 2019).

3.7. Controlled Release: An advantageous feature of biodegradable nanoparticles is their ability to release drugs in a controlled and sustained manner. Degradation of the nanoparticle matrix or drug diffusion through nanoparticle pores regulates drug release kinetics, allowing precise control over therapeutic effects and minimizing side effects (Hua et al., 2018).

3.8. Targeted Delivery: Surface modification of biodegradable nanoparticles with targeting ligands, such as antibodies, peptides, or aptamers, facilitates specific recognition and binding to target cells or tissues. This targeted delivery approach enhances nanoparticle accumulation at the site of action, improving therapeutic efficacy while minimizing off-target effects (Hua et al., 2018).

4. Contribution of Biodegradable nanoparticles to Sustainable Drug Delivery

Biodegradable nanoparticles are emerging as a game-changer in sustainable drug delivery, addressing many limitations of traditional methods and promoting environmental responsibility. Here's how they contribute:

4.1. Environmental Friendliness: Biodegradable nanoparticles contribute to sustainable drug delivery by utilizing materials that degrade into non-toxic byproducts, minimizing environmental pollution and ecological harm. Unlike non-biodegradable counterparts, biodegradable nanoparticles offer a greener alternative that aligns with principles of environmental stewardship and resource conservation (Danhier et al., 2012).

4.2. Reduced Waste: The biodegradability of nanoparticles reduces the accumulation of persistent waste in the environment and within biological systems. As biodegradable materials undergo degradation, they are metabolized or eliminated from the body, leading to reduced long-term impact on ecosystems and minimizing the need for waste management strategies associated with non-biodegradable materials (Mura et al., 2013).

4.3. Optimized Therapeutic Delivery: Biodegradable nanoparticles enable controlled and sustained release of therapeutic agents, prolonging their therapeutic effects and reducing the frequency of dosing. This optimized drug delivery approach enhances patient compliance, minimizes systemic toxicity, and improves overall therapeutic outcomes, contributing to sustainable healthcare practices (Alexis et al., 2008).

5. Synthesis Methods of Biodegradable Nanoparticles

Synthesis methods play a crucial role in the fabrication of biodegradable nanoparticles, influencing their physicochemical properties, drug loading capacity, and overall performance in drug delivery applications. Various synthesis methods are available for fabricating biodegradable nanoparticles, each offering unique advantages in terms of scalability, control over nanoparticle properties, and suitability for different types of materials and drugs. The choice of synthesis method depends on factors such as the desired nanoparticle characteristics, drug properties, and intended application in drug delivery (Table 1.). Some of the techniques commonly employed to synthesize biodegradable nanoparticles are summarized here:

5.1. Emulsification Method:

Emulsification is a widely used technique for preparing biodegradable nanoparticles, particularly polymer-based nanoparticles like PLGA and PLA. This method involves the dispersion of a polymer solution in an aqueous phase containing surfactants, followed by sonication or homogenization to form an emulsion. Subsequent solvent evaporation or solvent diffusion results in the formation of nanoparticles as the organic solvent evaporates, leaving behind polymer nanoparticles dispersed in the aqueous phase (Feng et al., 2016).

5.2. Nanoprecipitation Method:

Nanoprecipitation is another common method for synthesizing biodegradable nanoparticles, suitable for both polymer and lipid-based nanoparticles. In this method, a polymer or lipid solution is rapidly injected into an aqueous phase under stirring or sonication, leading to the formation of nanoparticles through the rapid diffusion and precipitation of the polymer or lipid material (Luo et al., 2019). The choice of solvent, polymer/lipid concentration, and processing parameters can be adjusted to control the size, morphology, and drug encapsulation efficiency of the nanoparticles.

5.3. Solvent Evaporation Method:

The solvent evaporation method is frequently used to prepare biodegradable nanoparticles, particularly those composed of polymers such as PLGA, PLA, and PCL. In this method, a polymer solution containing the drug of interest is emulsified in an aqueous phase containing surfactants to form an oil-in-water emulsion. Subsequent evaporation of the organic solvent under reduced pressure or at elevated temperatures results in the formation of solid nanoparticles suspended in the aqueous phase (Gong et al., 2018).

5.4. Self-Assembly Method:

Self-assembly techniques, including nanoprecipitation and solvent diffusion, can be utilized to fabricate biodegradable nanoparticles from amphiphilic block copolymers or lipid-based materials.

Amphiphilic block copolymers self-assemble into nanoparticles in aqueous solutions through the hydrophobic interactions between the polymer chains, forming a core-shell structure with a hydrophobic core and hydrophilic shell (Xiong et al., 2020). Similarly, lipid-based nanoparticles can self-assemble into various structures, including liposomes, micelles, and nanoemulsions, through the spontaneous organization of lipid molecules in aqueous environments (Li et al., 2018).

5.5. Electrospray Method:

Electrospray is an emerging technique for producing biodegradable nanoparticles with precise control over size, morphology, and drug loading. In this method, a polymer solution is subjected to an electric field, leading to the formation of a Taylor cone and the ejection of charged droplets. As the charged droplets travel towards a collector electrode, solvent evaporation occurs, resulting in the formation of solid nanoparticles with narrow size distribution (Yu et al., 2018).

6. Types of Biodegradable Nanoparticles

Biodegradable nanoparticles offer a versatile platform for drug delivery, with various types of materials being utilized for nanoparticle formulation. Here, we will discuss different types of biodegradable materials commonly employed in the synthesis of nanoparticles, including polymers and lipids, highlighting their unique properties and applications.

6.1. Biodegradable Polymer Nanoparticles:

Biodegradable polymers such as PLGA, PLA, PCL, and chitosan offer high biocompatibility, tunable properties, and controlled degradation kinetics. They can be tailored to achieve specific drug release profiles, target specific tissues, and minimize systemic toxicity. As biodegradable polymer nanoparticles have emerged as a game-changer in various fields, particularly drug delivery and tissue engineering, researchers are actively exploring their potential, with a focus on overcoming limitations and unlocking their full potential. Studies by Lembo, D. et al. (2017), demonstrated the effectiveness of these nanoparticles in encapsulating drugs, improving bioavailability, and reducing side effects. Zhao, Z. et al. (2020) explored their ability to target specific cells or tissues, further enhancing their therapeutic potential. Research by Nishiyabu, R. et al. (2009) emphasizes the biocompatible nature of self-assembled nanoparticles formed from certain polymers, making them suitable for various biomedical applications. A crucial aspect is controlling drug release. Freiberg, S., & Zhu, X. (2004) explored how manipulating polymer properties and formulation techniques can achieve a desired release profile, ensuring effective drug delivery over a sustained period. While effective, some studies, like those by Mora-Huertas, C. E. et al. (2010) highlight limitations in encapsulation efficiency. Researchers are actively exploring methods to improve this aspect. Bux, S. K. et al. (2010) acknowledged the need for cost-effective and scalable production techniques for large-scale applications. On the other hand, recent studies, like those by Dowling, P. et al. (2014), raised concerns about potential unintended effects, such as immune system activation or cardiovascular complications. Further research is necessary to fully understand and mitigate these potential risks.

6.2. Biodegradable Lipid Nanoparticles:

Biodegradable lipid nanoparticles (LNPs) are microscopic carriers, crafted from natural or synthetic lipids, that have revolutionized how we deliver therapeutic agents. Here we examine their key features, promising applications, and the latest research advancements, along with conclusions from different authors.

6.2.1 Unique Properties of Biodegradable LNPs:

LNPs are composed of lipids similar to those in cell membranes, making them readily broken down by the body, minimizing toxicity concerns (Maier, M. A. et al., 2013). This biocompatibility is a significant advantage over some synthetic polymer-based nanoparticles. The lipid bilayer structure offers superior encapsulation capabilities for a wide range of therapeutic agents, including hydrophobic drugs, hydrophilic drugs, and even nucleic acids (Allen, T. M., & Cullis, P. R. 2013). This versatility allows for the delivery of previously challenging therapeutic molecules. Formulation techniques and the properties of the lipids used can be tailored to control the release of the encapsulated cargo (Peer, D. et al., 2007). This enables sustained and targeted delivery, maximizing therapeutic efficacy and minimizing systemic exposure. LNPs can be modified with surface ligands that bind to receptors on target cells, enabling targeted delivery to specific tissues or organs (Torchilin, 2005). This approach minimizes off-target effects and improves treatment effectiveness.

6.2.2 Applications of Biodegradable LNPs:

Research groups worldwide are actively exploring the potential of biodegradable LNPs, as evidenced by these promising applications: **mRNA Delivery for Vaccines and Gene Therapy:** LNPs have played a pivotal role in the development of mRNA-based vaccines, such as those used against COVID-19. Studies by Ni et al. (2022) demonstrated the effectiveness of LNPs in delivering mRNA to cells, triggering the desired immune response. The potential for LNP-mediated delivery of mRNA for gene therapy applications is also under extensive investigation (Ball, R. L. et al., 2018). **Targeted Drug Delivery for Cancer Treatment:** Research by Xu, X. et al. (2015) explored the use of LNPs to deliver anticancer drugs to specific tumor sites. This targeted approach, as concluded by Xu, X. et al. (2015b), can potentially reduce systemic side effects and improve treatment outcomes. **Delivery of Hydrophobic Drugs:** LNPs are particularly adept at

encapsulating hydrophobic drugs that have poor water solubility. Studies by Hou, X. et al. (2021) demonstrated the use of LNPs to improve the bioavailability and efficacy of such drugs.

6.3. Other Biodegradable Nanoparticle Systems:

Biodegradable polymer and lipid nanoparticles have dominated the field of drug delivery, but the realm of possibilities extends far beyond these well-established platforms. Protein-based, carbohydrate-based, and nucleic acid-based nanoparticles, each offering unique advantages and promising applications.

Protein-based Nanoparticles:

Made from natural proteins like albumin or ferritin, these nanoparticles offer excellent biocompatibility and biodegradability. Their inherent biocompatibility minimizes immunogenic responses and allows for targeted delivery through specific protein-protein interactions. Protein-based nanoparticles are being explored for drug delivery, enzyme replacement therapy, and even imaging applications due to their inherent targeting capabilities (Hong, S. et al., 2020). Studies by Neek, M. et al. (2019) demonstrated their potential for targeted delivery of cancer drugs. Scaling up production and controlling protein structure during nanoparticle formation remain hurdles that researchers are actively addressing.

Carbohydrate-based Nanoparticles:

Carbohydrate-based Nanoparticles are developed from natural sugars like chitosan or dextran, these nanoparticles offer biocompatibility, biodegradability, and unique surface properties (Marradi, M. et al., 2011). Their mucoadhesive properties allow for extended residence time at mucosal surfaces, making them ideal for applications like nasal or oral drug delivery (Verma, M. L. et al., 2020). Studies by Bhumkar, D. R. et al. (2007) explored the use of chitosan nanoparticles for nasal insulin delivery. Beyond drug delivery, carbohydrate-based nanoparticles hold promise for vaccine development and gene therapy due to their ability to act as adjuvants, enhancing immune response (Marradi, M. et al., 2011). However, encapsulation efficiency and controlled release profiles require further optimization for broader applicability (Verma, M. L. et al., 2020).

Nucleic Acid-based Nanoparticles:

Formed from DNA or RNA, these nanoparticles offer a unique platform for gene delivery and gene silencing. Their inherent ability to interact with cellular machinery positions them perfectly for delivering genetic material for therapeutic purposes (Li, W., & Szoka, F. C. 2007). Nucleic acid-based nanoparticles are actively explored for gene therapy in various diseases, including cystic fibrosis and cancer (Yin, H. et al., 2014). Studies by Chalbatani, G. M et al. (2019) demonstrated their potential for delivering siRNA (small interfering RNA) for cancer therapy. Delivery efficiency and potential off-target effects require careful consideration and ongoing research (Campuzano, S. et al., 2018).

7. Drug loading into biodegradable nanoparticles

Drug loading into biodegradable nanoparticles is a crucial step in the formulation of drug delivery systems, determining the efficiency and effectiveness of drug delivery. Here's an overview of the methods commonly used for drug loading into biodegradable nanoparticles:

7.1. Physical Entrapment: The drug is encapsulated within the nanoparticle matrix during the formation of the nanoparticles. Physical entrapment is a widely used method for loading drugs into biodegradable nanoparticles. It involves incorporating the drug into the nanoparticle matrix during the formation of the nanoparticles (Rao, K. 2014a, Rao, K. 2014b). Here's a detailed look at the process (Liu, Y et al., 2020):

1. Preparation of Nanoparticles: The first step is the preparation of the nanoparticles themselves. This can be done through various methods such as emulsion, solvent evaporation, or nanoprecipitation. During this process, the polymer that forms the nanoparticles is dissolved in a solvent.

2. Incorporation of the Drug: The drug is mixed with the polymer solution before or during the formation of the nanoparticles. As the nanoparticles form, the drug becomes entrapped within the polymer matrix.

3. Solidification: The solvent is then removed, often through evaporation or a washing step, leading to the solidification of the nanoparticles with the drug physically entrapped within them.

4. Drug Loading and Entrapment Efficiency: The amount of drug that is loaded into the nanoparticles is quantified as drug loading (DL), which is the mass ratio of drug to drug-loaded nanoparticles. Entrapment efficiency (EE) is another important parameter that describes the efficiency of the preparation method to incorporate the drug into the carrier system. It is defined as the experimental drug loading divided by the nominal drug loading, expressed as a percentage (Judefeind, A., & De Villiers, M. M. 2009).

7.2. Adsorption: Drugs are adsorbed onto the surface of nanoparticles after their formation. Thus, adsorption method for drug loading into biodegradable nanoparticles is a surface-based technique where the drug molecules are adsorbed onto the surface of nanoparticles after their formation (Rao, K. 2014a). Adsorption is particularly useful for loading drugs that are poorly soluble or unstable within the polymer matrix (Sumana, M. et al., 2020). It's also used when a burst release of the drug is desired. The manufacturing process as reviewed time to time is given below (Gagliardi. et al., 2021, Varalakshmi et al., 2022):

1. Nanoparticle Formation: First, biodegradable nanoparticles are formed using methods like emulsion, solvent evaporation, or nanoprecipitation. These nanoparticles are made from polymers

that can degrade within the body, such as PLGA (poly(lactic-co-glycolic acid)).

2. Drug Adsorption: After the nanoparticles are formed, the drug is introduced in a solution where it adsorbs onto the surface of the nanoparticles. This process can be influenced by factors such as the charge and hydrophobicity of the drug and the nanoparticle surface, as well as the solvent used.

3. Optimization: The adsorption process can be optimized by adjusting parameters like the pH and ionic strength of the solution, the temperature, and the incubation time to maximize drug loading.

7.3. Chemical Conjugation: Drugs are chemically bonded to the nanoparticle surface or matrix. Chemical conjugation for drug loading into biodegradable nanoparticles is a method that involves creating a covalent bond between the drug molecule and the nanoparticle. This technique ensures that the drug is firmly attached to the nanoparticle, which can be beneficial for targeted drug delivery and controlled release. Chemical conjugation is particularly useful in the development of drug delivery systems for diseases like cancer, where targeted delivery and controlled release are critical for treatment effectiveness (Eras, et al. 2022, Tripathi, et al., 2022, Fasiku et al., 2021). This method is part of a broader strategy to improve the pharmacokinetics and pharmacodynamics of drugs, aiming to maximize therapeutic efficacy while minimizing side effects . Here's an overview of the process:

1.Selection of the Drug and Nanoparticle: A suitable drug is chosen along with a biodegradable nanoparticle, often made from materials like PLGA (poly(lactic-co-glycolic acid)).

2. Functionalization of the Nanoparticle: The nanoparticle surface is chemically modified to introduce functional groups that can react with the drug molecule.

3. Conjugation of the Drug: The drug is then chemically bonded to the functionalized nanoparticle through a covalent bond. This step may involve the use of linkers or coupling agents to facilitate the reaction.

4. Purification: After conjugation, the nanoparticles are purified to remove any unreacted drug or by-products.

7.4. *Ionic Interaction*: Drugs are loaded through electrostatic interactions with the nanoparticle material. The ionic interaction method for drug loading into biodegradable nanoparticles is a technique that relies on the electrostatic attraction between charged drug molecules and charged nanoparticles (Judefeind, A., & De Villiers, M. M. 2009). Here's a step-by-step explanation of the process:

1. Preparation of Charged Nanoparticles: Biodegradable nanoparticles are prepared with a net charge, either positive or negative, using polymers like chitosan (positively charged) or alginate (negatively charged).

2. Drug-Nanoparticle Interaction: The drug, which carries an opposite charge to the nanoparticles, is introduced in a solution. Due to the electrostatic attraction, the drug molecules will bind to the surface of the nanoparticles (Varalakshmi et al., 2022).

3. Ionic Gelation: This is a common technique used in conjunction with ionic interactions. It involves adding a cross-linking agent to the solution, which leads to the gelation of the polymer and the formation of a stable nanoparticle-drug complex.

The ionic interaction method is particularly useful for loading drugs that have a strong ionic character and for applications where controlled release and targeted delivery are desired. It's a versatile technique that can be adapted to a wide range of drugs and targeting Strategies (Blanco-Cabra et al., 2022). .

Factors Influencing Drug Loading:

The efficiency of drug loading into biodegradable nanoparticles is influenced by a variety of factors. Understanding these factors is crucial for optimizing the drug loading process and ensuring the effectiveness of the drug delivery system (Chart 1). These factors collectively determine the drug loading content and release mechanism of biodegradable nanoparticles.

Various factors impact drug delivery systems, categorized into polymer characteristics, drug properties, nanoparticle features, and process parameters. Polymer characteristics, such as molecular weight, composition, and hydrophobicity/hydrophilicity, affect drug loading capacity and release. Drug properties, including solubility, stability, and molecular size, determine how well the drug integrates into the system (Ribeiro, C et al., 2017). Nanoparticle features, like size, surface charge, and porosity, influence drug loading efficiency and interactions. Process parameters, such as solvent choice, mixing speed, and temperature, play crucial roles in nanoparticle formation and drug loading efficacy (Madkhali, O. A. 2023, Su, S., & Kang, P. M. 2020). Achieving the desired release rate is a major challenge. Ensuring stability under physiological conditions is crucial for effective drug delivery. Maintaining quality during scale-up is essential for commercial viability (Mahapatro, A., & Singh, D. K. 2011).

The Release Mechanisms:

Release mechanisms in drug delivery systems are critical for ensuring that the drug is released at the right place, at the right time, and in the right amount. Diffusion, where the drug moves from higher to lower concentration within the nanoparticle, is influenced by factors like molecular size and concentration gradient. Degradation occurs as the polymer matrix of the nanoparticle breaks down over time, releasing the drug, often catalyzed by enzymatic activity (Ribeiro et al., 2017). Swelling of nanoparticles in response to water absorption increases the spacing between

polymer chains, facilitating drug diffusion. Osmosis, erosion, and chemical reactions also contribute to drug release, with external stimuli like temperature changes or magnetic fields triggering release in thermo-responsive or magnetic nanoparticles. Combining these mechanisms enables tailored release profiles, allowing for sequential release of multiple drugs or controlled release over time. These diverse mechanisms offer versatility in designing drug delivery systems to meet specific therapeutic needs, improving treatment efficacy and patient outcomes (Ge et al., 2011, Sanopoulou, M., & Papadokostaki, K. G. 2017).

These mechanisms can be engineered to create controlled-release systems that deliver the drug over an extended period, reduce the frequency of administration, and improve patient compliance. The choice of mechanism depends on the drug's properties, the desired release profile, and the target site within the body(Ge et al., 2011, Sanopoulou, M., & Papadokostaki, K. G. 2017, Ding, C. et al., 2016). Controlled release systems have been developed to improve the temporal and spatial presentation of drugs in the body, protect drugs from physiological degradation or elimination, enhance patient compliance, and add commercial value to marketed drugs by extending patent protection[1]. Understanding these mechanisms is crucial when designing and manufacturing controlled-release systems, and in identifying potential failure modes (Siegel, R. A., & Rathbone, M. J. 2011).

The kinetics of drug release can follow zero-order, first-order, or more complex patterns depending on the delivery system[2]. Sophisticated systems like pulsatile-release delivery systems, which have rapid and transient release of a certain amount of drug within short time periods preceded by predetermined off-release periods, can also be designed[2].

8. Biocompatibility and Safety

Biocompatibility and safety are paramount concerns when it comes to the use of biodegradable nanoparticles in medical applications. Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific application. In the context of nanoparticles, it means they should not elicit a significant immune or inflammatory reaction when introduced into the body (Elmowafy et al., 2019). The biocompatibility of nanoparticles is assessed through a series of in vitro and in vivo tests that evaluate cytotoxicity, genotoxicity, immunogenicity, and overall systemic toxicity. Nanoparticles can potentially be toxic due to their size, shape, surface charge, and composition. They may cause oxidative stress, inflammation, or even cellular damage if not designed properly. As biodegradable nanoparticles break down, their degradation products must also be non-toxic and safely cleared from the body (Kučuk et al., 2023). Poly(lactic acid) and poly(lactic-co-glycolic acid) are among the FDA-approved polymers used for safe drug delivery systems. They are known for their excellent biocompatibility, controllable biodegradability, and high safety profiles (Ranjha et al., 2021). Surface modification of nanoparticles can be used to enhance biocompatibility and reduce potential toxicity. This includes coating with biocompatible materials or adding targeting ligands to direct the nanoparticles to specific tissues. The biodegradation rate of nanoparticles is crucial for safety. It must be controlled so that the nanoparticles do not accumulate in the body and are broken down into non-toxic by-products that can be excreted (Kyriakides et al., 2021). There are established standards and guidelines for evaluating the biocompatibility and safety of medical devices, including nanoparticles, which must be rigorously followed. Even after approval, the safety and biocompatibility of nanoparticles must be continuously monitored to ensure no long-term adverse effects occur (Kučuk et al., 2023).

Ongoing research is focused on improving the design and functionality of nanoparticles to address any safety concerns and enhance their therapeutic efficacy.

Toxicity and Compatibility of biodegradable Nanoparticles

Biodegradable nanoparticles (NPs) offer a promising advancement in various fields due to their unique properties and potential for environmental friendliness. However, their interaction with biological systems necessitates careful consideration of both their toxicity and compatibility. Biodegradable NPs are designed to break down in the environment, minimizing the risk of long-term accumulation and potential toxicity compared to traditional, non-degradable NPs. Studies like the one on lignin nanoparticles have shown minimal impact on microorganisms, suggesting good biocompatibility (Zhong, et al., 2014). Despite biodegradability, the degradation products themselves might have unforeseen effects. The size, shape, and surface properties of NPs can influence their interaction with cells and tissues, potentially leading to unintended consequences (Gautam, A., & Van Veggel, F. C. J. M. 2013). Different types of biodegradable materials will have varying toxicity profiles. The intended use of the NPs will influence the level of biocompatibility required. Rigorous testing is essential to assess the potential risks associated with each specific type of biodegradable NP. By carefully considering these factors, researchers and developers can harness the potential of biodegradable NPs while minimizing their potential downsides (Elmowafyet al., 2019). Assessing the toxicity and compatibility of biodegradable nanoparticles (NPs) with biological systems is crucial for their safe use in clinical and environmental applications. Table 3. describes some methods and approaches for assessing the toxicity and compatibility of biodegradable nanoparticles (NPs) with biological systems (George et al., 2009, Thomas, et al. 2023).

9. Applications in Targeted Drug Delivery

Targeted drug delivery is a critical area in medicine, aiming to enhance therapeutic efficacy while minimizing side effects.

Biodegradable nanoparticles (NPs) play a pivotal role in achieving this goal. Here are some of their applications:

9.1. Site-Specific Drug Delivery:

Biodegradable NPs can be engineered to carry drugs directly to the desired site of action. For instance,

Cancer Therapy: NPs loaded with chemotherapeutic agents can selectively accumulate in tumor tissues due to the enhanced permeability and retention (EPR) effect. This minimizes damage to healthy cells. Conventional cancer treatments often suffer from poor drug targeting, leading to severe side effects on healthy tissues. Biodegradable nanoparticles (NPs) emerge as a promising strategy for site-specific drug delivery, offering several advantages. Tumors have leaky vasculature, allowing NPs to passively accumulate within the tumor site (Farokhzad, et al., 2006). NPs can be functionalized with specific ligands (antibodies, peptides) that recognize and bind to cancer cells, promoting targeted drug delivery (Shargh et al., 2016). Biodegradable NPs can be designed to release their cargo in a controlled manner, either triggered by the tumor microenvironment (pH, enzymes) or external stimuli (light, ultrasound) (Mondal et al., 2023). Selection of biocompatible and biodegradable polymers (e.g., PLGA, chitosan) for minimal long-term toxicity (Mahapatro, A., & Singh, D. K. 2011). Encapsulation of the anticancer drug within the NP matrix or attached to its surface. Optimization of NP size (typically 10-200 nm) for efficient tumor penetration and EPR effect (Tiwari et al., 2012). Utilizing the EPR effect for preferential accumulation in tumors due to leaky vasculature (Farokhzad, et al., 2006). Active targeting is attaching targeting moieties (antibodies, peptides) to the NP surface that bind to specific receptors on cancer cells, promoting targeted delivery and reducing off-target effects (Shargh et al., 2016).

Designing NPs to degrade in response to the tumor microenvironment (e.g., acidic pH) for localized drug release (Mondal et al., 2023). Incorporating stimuli-responsive materials for controlled release triggered by external factors like light or ultrasound (Mondal et al., 2023).

Inflammatory Diseases: Inflammatory diseases are characterized by localized inflammation in specific tissues. Traditional treatments often have limited targeting and can cause unwanted side effects in healthy organs. NPs can target inflamed tissues (e.g., arthritic joints) by exploiting local changes in blood vessels and immune cell activity. Biodegradable nanoparticles (NPs) offer a promising approach for site-specific drug delivery in these conditions, providing several advantages like, targeted Drug delivery where NPs can be engineered to deliver anti-inflammatory drugs directly to the inflamed site, reducing systemic exposure and potential side effects (Sinhmar, G. K. et al., 2018), controlled release where biodegradable NPs can be designed to release their cargo in a controlled manner over time, potentially reducing dosing frequency and improving treatment compliance (Lamprecht, A et al., 2001) and modulating the Immune Response where NPs can be used to deliver immunomodulatory drugs that can dampen the inflammatory response at the source (Wang H et al., 2021, Chuan, Y. P. et al., 2012). The key points in this approach include,

1. NP design and targeting, where selection of biocompatible and biodegradable polymers (e.g., PLGA, chitosan) for minimal long-term effects (Li, M et al., (2023),
2. Encapsulation of the anti-inflammatory drug within the NP or conjugated to its surface,
3. Functionalization of the NP surface with ligands (antibodies, peptides) that specifically target inflamed tissues (Sinhmar, G. K. et al., 2018). For instance, NPs loaded with corticosteroids can be targeted to inflamed joints, potentially reducing systemic steroid exposure and associated side effects (Nasra, S. et al., 2022)
4. NPs designed for oral delivery can release drugs specifically in the inflamed intestine, improving efficacy and reducing gut irritation (Zhang M et al., 2018). Designing NPs to degrade in response to the inflammatory microenvironment (e.g., reactive oxygen species) for localized drug release (Lamprecht, A et al., 2001).
5. Utilizing pH-sensitive materials for controlled release in the acidic environment of inflamed tissues (Gao W et al., 2010).

C. Brain Disorders: Brain disorders pose a significant challenge due to the presence of the blood-brain barrier (BBB), which restricts the passage of most drugs from the bloodstream into the brain. NPs can cross the blood-brain barrier, delivering drugs to the brain for treating neurodegenerative diseases or brain tumors. Biodegradable nanoparticles (NPs) offer a promising approach for site-specific drug delivery in these conditions for instance,

a) **Overcoming the Blood-Brain Barrier (BBB):** NPs can be engineered to bypass or penetrate the BBB, delivering drugs directly to the affected brain region (Annu et al., 2022).

b). **Targeted Delivery:** NPs can be functionalized with specific ligands to target diseased neurons or specific cell types within the brain (Thomsen, L. B et al., 2015).

c). **Controlled Release:** Biodegradable NPs can be designed to release their cargo in a controlled manner within the brain, potentially improving treatment efficacy and reducing systemic side effects (Gagliardi A, et al., 2021).In this approach The biocompatible and biodegradable polymers (e.g., PLGA) that can degrade in the brain environment are selected (Montegiove N et al., 2022).

This is followed by encapsulation of the therapeutic agent within the NP or conjugated to its surface. The strategies to bypass the BBB involve surface modification with ligands that promote receptor-mediated transcytosis across the BBB endothelial cells (Sharma, G et al., 2019) then the ultra-small NPs (less than 20 nm) that may passively diffuse through the BBB (Levin J. 2017). The targeted delivery strategy is followed by attaching targeting moieties (antibodies, peptides) to the NP surface that specifically bind to

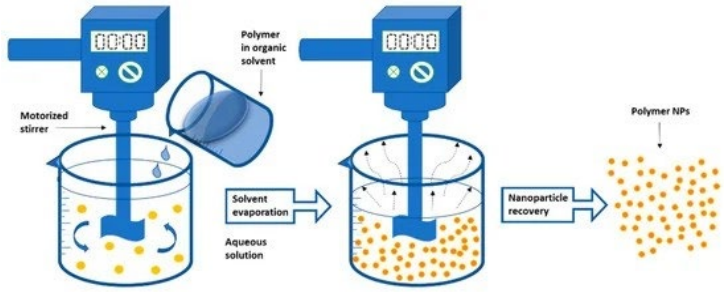

Figure 1. Schematic illustration of the solvent evaporation procedure. (Source: Pulingam et al., 2022).

Table 1. Comparing and contrasting different synthesis approaches of Biodegradable Nanoparticles.

Synthesis Approach	Principle	Advantages	Disadvantages	Applications	References
Emulsification Method	Mixing two immiscible phases with a stabilizer	Simple and scalable	High energy input	Drug delivery, Cosmetics, Food Industry	Jenjob R et al., 2019
Nanoprecipitation Method	Rapid mixing of organic and aqueous phases	High encapsulation efficiency	Use of organic solvents	Gene therapy, Drug delivery, Tissue engineering	Yadav KS et al., 2010
Solvent Evaporation Method	Dissolving polymer and drug in solvent, followed by solvent evaporation	Controllable particle size	Residual solvent traces	Imaging, Encapsulation, Agriculture	Jiang, J. et al., 2018
Self-Assembly Method	Spontaneous organization of molecules into ordered structures	Biocompatible materials	Limited control over morphology	Tissue engineering, Drug delivery, Diagnostics	Whitesides, G. M et al., 2006
Electrospray Method	Applying high voltage to a polymer solution to generate droplets	Narrow size distribution	Need for specialized equipment	Controlled release, Drug delivery, Inhalation therapy	Sridhar R, Ramakrishna S. et al., 2013

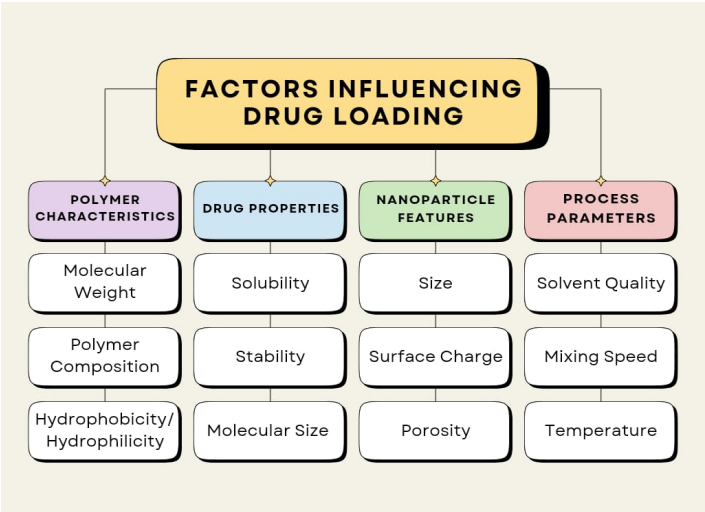

Chart 1. Essential Factors Influencing Drug Delivery Systems.

Table 2. Biodegradable Polymers for Nanoparticle Applications (Kumari, A. et al., (2010), Alaswad SO et al., (2022), Soppimath, K. S. et al., (2001) and Bharadwaz, A., & Jayasuriya, A. C. (2020).

Polymer	Biocompatibility	Tunable Properties	Controlled Degradation Kinetics
PLGA (Poly(lactic-co-glycolic acid))	Well-established, Generally non-toxic	Lactid to glycolic acid ratio controls degradation rate, hydrophobicity, and mechanical strength	Faster degradation with higher glycolic acid content
PLA (Polylactic acid)	Good biocompatibility	Molecular weight, crystallinity, and processing methods influence mechanical properties, drug release, and degradation rate	Slower degradation compared to PLGA
PCL (Polycaprolactone)	Excellent biocompatibility, Low inflammatory response	Crystallinity and molecular weight affect hydrophobicity, mechanical properties, and degradation rate	Slowest degradation rate among these polymers
Chitosan (Natural polysaccharide)	Biocompatible, Biodegradable, Mucoadhesive properties	Molecular weight, degree of deacetylation (%), and processing methods influence encapsulation efficiency, drug release, and gelation properties	Degradation rate depends on factors like pH and enzymatic activity

Table 3. Toxicity and Compatibility of Biodegradable Nanoparticles (NPs)

Method/Approach	Focus	Advantages	Disadvantages
In vitro studies	Cellular and molecular level effects	Controlled environment. High throughput screening possible. Less ethical concerns than in vivo studies.	Limited representation of complex biological systems. Potential artifacts due to isolated cell cultures
Cell viability assays	Measure cell death or proliferation	Simple and reliable. Provides information on cytotoxicity	May not reflect in vivo effects
Reactive Oxygen Species (ROS) assays	Detect oxidative stress caused by NPs	Indicates potential for cellular damage	Not specific to NP exposure
Gene expression analysis	Identify changes in gene expression due to NP exposure	Offers insights into cellular response mechanisms	Requires specialized techniques and interpretation
In vivo studies	Whole-organism response to NPs	More realistic assessment of toxicity. Allows for investigation of biodistribution and excretion	Ethical considerations. Higher cost and time compared to in vitro studies
Histopathology	Examination of tissue structure for signs of damage	Provides detailed information on organ and tissue effects	Requires sacrificing animals
Blood tests	Analyze changes in blood cell counts and markers of inflammation	Indicates potential for systemic effects	May not be specific to NP exposure
Physicochemical characterization	Analysis of NP size, shape, surface charge, and degradation rate	Crucial for understanding NP behavior and potential interactions with biological systems	Requires specialized equipment and expertise
Computational modeling	Simulation of NP-cell interactions	Can predict potential risks and guide further testing	Relies on accurate input data and may not fully capture biological complexity

Author contributions

K.H. led the study's design, conceptualization, and manuscript preparation. M.R. was responsible for data collection and analysis. M.S.S.K. contributed to the interpretation of the results and provided critical revisions. T. assisted in final manuscript editing. All authors discussed the results and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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