Development of Eco-Friendly Nanoparticles for Sustainable Drug Delivery: A Comprehensive Review

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Abstract:

The need for biodegradable nanoparticles as part of environmentally friendly drug delivery has grown tremendously over the years. These nanoparticles have several advantages biocompatibility, low toxicity, and rather minimal negative effects on the environment due to their lipid, protein, and polysaccharide origin. Some common examples of such systems are referred to in the following section to exemplify the versatility of their application. Computer-aided mechanisms including molecular modeling, simulation of nanodevice, and high-end computing are essential to nanoparticle design. These approaches afford accurate prediction of the nanoparticle's actions, high load with the drug, precise release, and improved interactions of nanoworld with biological systems. In this regard, there is still a long way to go in reaching large-scale industrial applications of biodegradable nanoparticles due to problems related to the reproducibility, efficiency, and cost of these nanocarriers, as well as the compliance of industrial products with the relevant national and international standards. Green synthesis techniques and computational methods used in the synthesis process offer themselves as possible solutions to these challenges as progress in the quest for economic and environmentally friendly solutions is made. From this review, it can be seen that there are tremendous opportunities for biodegradable material and computation in an enhanced green drug delivery system. Solving current issues will thus create a way for the integration of green nanoparticles into the life of healthcare facilities and the general environment for health improvement.

Keywords: Eco-Friendly Nanoparticles, Computer Simulation, Nanoinformatics, Poly- d, l-lactide-co-glycolide (PLGA), Healthcare Innovations, Poly-e-caprolactone (PCL), Polylactic Acid (PLA).

1. Introduction:

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Taniguchi in 1974, introduced the term ‘nanotechnology’. The scientific concept was first presented by Nobel Laureate Richard Feynman during his 1959 famous lecture. Professor Richard Feynman won the Nobel Prize for his 1959 speech named 'There’s Plenty of Room at the Bottom'. Manipulation, reduction, and fabrication of materials in nanotechnology are involved. Their capabilities to enhance bioavailability stretch across the realm of controlled sustained drug release and high drug payload capacity. They additionally help drugs penetrate cells. These systems hold large amounts of drugs with appropriate properties to enter cells effectively, achieve sites or organ targeting, protect drugs from physiological environments, and support various administration routes including parenteral, oral, nasal, and intraocular deliveries, nanoparticles especially prove to be important in disease prevention and disease treatment, delivering drugs [1,2]. The increase in the demand for sustainable and efficient drug delivery systems has led to the advancement of pharmaceutical sciences. Drug delivery systems (DDS) are widely studied and aim to improve the efficacy and administration of pharmaceutical products, such as drugs, antigens, enzymes, vaccines, etc. [3]. Although these conventional drug delivery systems have wide application, they suffer from many limitations such as limited bioavailability, fluctuations in plasma concentration, lack of selectivity, first-pass metabolism, instability, large residues, failure to address the above problems of high drug concentration in the target site, variety of controlled drug release, etc. [4,5]. Most of the conventional drug delivery systems are based on the usage of non-biodegradable materials which play a major role in increasing medical waste and would contribute to environmental pollution which is a health hazard. In response to these noted challenges, efforts to exploit biodegradable nanoparticles demonstrate the promise of improving both therapeutic outcomes and reducing environmental concerns [3,4]. Using sustainability principles to integrate them into drug delivery systems is necessary to lower the environmental impact and to ensure long-term sustainability. The biodegradable nanoparticles, which are made from biocompatible polymers or lipid-based materials, are a promising solution because they can break down into nontoxic byproducts. This green feature limits environmental damage and answers questions about the accumulation of non-biodegradable materials in nature [6]. In addition to this, the use of eco-friendly synthesis techniques and renewable resources provides additional means for the sustainability of nanoparticle-based drug delivery systems. These systems also provide environmental benefits, efficiency in energy use and cost-effective healthcare [9]. Additionally, the design and optimization of these nanoparticles are enabled by the advent of advanced computational tools that allow one to critically control their physicochemical properties, surface modifications, as well as their kinetics of drug release.

2. Biodegradable Nanoparticles in Drug Delivery:

Biodegradable nanoparticles have drawn much interest in drug delivery research, thanks to their many advantages, namely biocompatibility, reduced toxicity, and environmentally sustainable nature [7, 8]. These encapsulating nanoparticles, which are made from lipids,

proteins, and polysaccharides, offer an efficient platform for encapsulating therapeutic agents as well as enabling controlled or sustained release of these agents whilst reducing the occurrence of their adverse effects. In the past few years, biodegradable nanotechnology has expanded to greener and more sustainable methodologies. However, most syntheses observed in previous work relied on toxic chemicals and hazardous organic solvents [9,10] with the potential for environmental and biological incompatibility. As a result, however, alternative synthesis routes involving green nanotechnology can employ eco-friendly reducing agents including citrate, ascorbic acid, and plant extracts [11,12]. In addition to reducing toxicity, they increase the biocompatibility and stability of the nanoparticles and are suitable for use in a variety of applications including drug delivery [13].

2.1. Poly- d, l-lactide-co-glycolide (PLGA): Poly- d, l -lactide-co-glycolide (PLGA) is a highly used biodegradable polymer system in the realm of nanomedicine. Inside the body, hydrolysis transforms the substance into two metabolites, lactic acid along with glycolic acid, which are both biodegradables along with being easily treated by physiological processes. The breakdown products from hydrolysis minimize toxic effects of the polymer both in systemic applications and when used as a biomaterial for drug delivery. Researchers primarily utilize four synthetic approaches, namely emulsification diffusion [14], solvent emulsion evaporation [15], interfacial deposition, and nanoprecipitation [16], to create PLGA nanoparticles.

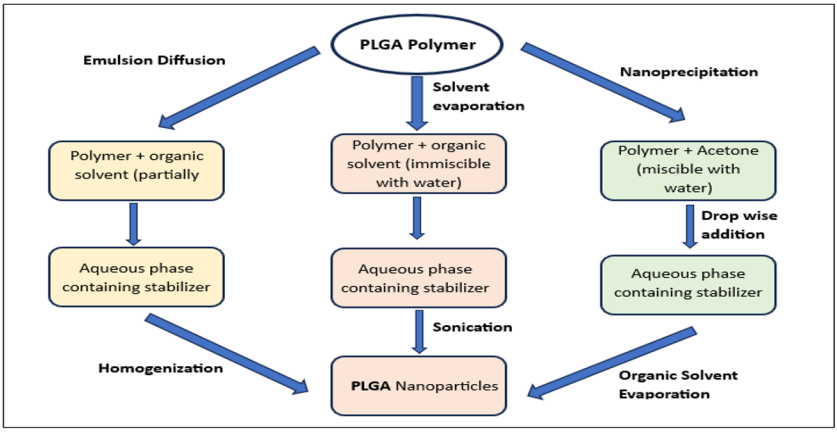

Figure 1: Different method of synthesis of PLGA Nanoparticles

The production of PLGA polymers requires dissolving them in an organic solution before emulsifying them in aqueous conditions containing stabilizers through homogenization to achieve the emulsification-diffusion process. In addition, the solvent evaporation approach works by dissolving PLGA in volatile organic solvents such as DCM, acetone, or $CHCl_3$, which is then added to fresh stirring water and reduced pressure for solvent evaporation. The nanocapsules and nanospheres can be formed using interfacial deposition methods,

allowing the nanoparticles to be deposited at the air-water interface as well as at the air–miscible organic solvent interface. However, the most used of these techniques is nanoprecipitation, which involves adding acetone-dissolved PLGA dissolving PLGA with an increasing rate into an isosmotic counterstream. PLGA nanoparticles have exhibited great efficacy in nanomedical development for targeting proteins, peptides, vaccines, growth factors, antigens, and gene delivery mechanisms [17,18,19]. Both drug release rates and therapeutic effectiveness are largely influenced by the formulation parameters, such as the lactide to glycolide monomer ratio, particle size distribution, and surface modification [20]. Acidic metabolites from PLGA may compromise the stability of certain bioactive compounds, except that PLGA was combined with other polymers such as alginate or chitosan [21,22]. Additionally, approval for human use from the U.S. Food and Drug Administration (FDA) – a requirement for the use of PLGA [23], has been granted for several formulations containing this polymer, which have already won commercial endorsements for treating several medical conditions.

The table given below provides an overview of PLGA Poly(lactic-co-glycolic acid)) biodegradable polymeric nanoparticles utilized for drug delivery. It summarizes different encapsulated drugs, their encapsulation efficiency (EE), methods of synthesis, therapeutic improvements, release mechanisms, in vivo results, and references. The data shows us the various uses of PLGA nanoparticles in controlled drug release, enhanced therapeutic efficacy, and improved drug targeting across various compounds.

Table 1: Poly (lactic-co-glycolic acid) PLGA biodegradable polymeric nanoparticles for drug delivery

Polymer	**Encapsulant**	**EE**	**Method of Synthesis**	**Therapeutic Improvement**	**Release mechanism**	**In vivo**	**Reference**
PLGA Poly (lactic-co-glycolic	9-Nitrocamptothecin	33 %	Nanoprecipitation	Control release up to 160 h	Diffusion	-	24
	Paclitaxel	>90 %	Interfacial Deposition	Antitumoral efficacy improved as compare	Diffusion, Dissolution	After incubation for 24h, viability against NCL-H69 in	25

acid)				d to free drug		cell reduced to 30%	
	Docetaxel	87.3%	Emulsion Solvent Diffusion	Superior cellular uptake over non-modified particles	Matrix erosion, Diffusion	Increased intracellular uptake in folate receptor-positive cancer cells	26
	Thymopentin	31.03 %	Double Emulsion Solvent evaporation	Intestinal bio adhesion enhanced	Diffusion	Large number of nanoparticles is found in small intestine	27
	Dexamethasone	6%	Solvent evaporation method	Slow drug release up to 50h	Diffusion	-	28
	Xanthones	77 %	Solvent displacement	Slow drug release up to 4h	Partition between the external aqueous medium and the oil core	-	29
	Taxol	70 %	Nanoprecipitation	Inhibit tumor growth	Diffusion	More cytotoxic on Hela cells than taxol	30

2.2. Polylactic Acid (PLA): It is a thermoplastic aliphatic polyester derived from renewable biomass resources and categorized by its biocompatibility and biodegradability – the

material is eliminated through metabolism and hydrolyzation by the body into L-lactic acid. PLA nanoparticles have been synthesized using various techniques.

Poly (lactic acid) (PLA) nanoparticles contribute to drug delivery systems while demonstrating potential benefits for clinical results. The table given below shows different compounds encapsulated in PLA alongside their significant encapsulation efficiencies achieved through several synthesis approaches. A drug delivery system using Poly(lactic acid) nanoparticles results in five significant benefits, including a duration of drug release exceeding seven days and enhanced pharmacological availability in addition to diminished damage to organs and directed transport capabilities. Plasma levels and improved delivery outcomes supported by in vivo research highlight how nanoparticles from PLA reduce medication accumulation throughout non-ideal organs while increasing blood absorption rates and maintaining drug stability.

Table 2: Polylactic Acid (PLA) biodegrdable polymeric nanoparticles for drug delivery

Polymer	Encapsulant	EE	Method of synthesis	Therapeutic Improvement	Release mechanism	In vivo	Reference
Polylactic acid (PLA)	Hemoglobin	87.9%	Double emulsion	Less uptake of evaporation	Diffusion	Reduction in liver accumulation	31
	Ellagic acid	50%	Emulsion diffusion evaporation	Improved oral evaporation	Diffusion degradation	Nanoparticles mitigated cyclosporin-induced nephrotoxicity in rats	32

	Bovine serum albumin (BSA)	75.6%	Double emulsion	Blood circulation time increases	Poly degradation, Diffusion of the protein entrapped	Uptake observed in both NIH-3T3 and caco -2cell lines	33
	Oridonin	91.8%	Solvent diffusion	Slow release of drugs up to 72 h	Diffusion	Maintained high concentrations of Oridonin in the liver, lungs, and spleen, with reduced distribution in the kidneys	34
	Dexamethaxone	6%	Spray drying	Slow release of drug up to 50h	Diffusion	-	35

	Savoxepine	95%	Salting out	Controlled release of drug up to 1week	Diffusion	Prolonged plasma levels following intramuscular and intravenous administration	36
	Progesterone	70%	Solvent evaporation	-	Diffusion	-	37

2.3. Poly-e-caprolactone (PCL): Being biodegradable, poly-e-caprolactone (PCL) has vital applications as the carrier material in drug delivery systems by its hydrolytic degradation under physiological conditions. PCL stands out as a polymer for long-term implantable device development because it degrades slowly and exists in the body for an extended period compared to polylactide. The production of PCL nanoparticles relies mainly on solvent displacement, solvent precipitation and solvent evaporation methods. The synthesis of therapeutic molecules was successful using poly-e-caprolactone nanoparticles for increasing their therapeutic benefits.

Table 3: Poly-e-caprolactone (PCL) biodegradable polymeric nanoparticles for drug delivery

Polymer	**Encapsulant**	**EE**	**Method of synthesis**	**Therapeutic Improvement**	**Release mechanism**	**In vivo**	**Reference**
Poly-e-caprolactone (PCL)	Tamoxifen	90%	Solvent displacement	Select tumor targeting with a circulatio	-	Time dependent drug accumulation	38

				n drugs reservoir		within the tumor and prolonged circulation	
	Clonazepam	72.6 - 95.1 %	Solvent evaporation	Drugs release behavior can be regulated by incorporating thermosensitive polymers	Diffusion	-	39
	Taxol	20.79%	Micelles	Higher taxol loading	-	Reduced fasting glycemia in a dose dependent manner, with nanoparticles exhibiting strong adhesion to intestinal mucosa	40

	Insulin	96%	-	Preservation of insulins' biological activity	Diffusion	-	41
	Saquinavir	60%	Solvent displacement	Concentration of intracellular saquinavir concentration	Diffusion	Rapid cellular uptake of rhodamine -123 encapsulated in PEO-PCL nanoparticles was observed in THP 1 cells	42
	Docetaxel	90%	Nanoprecipitation	Antitumor effect increases	Diffusion	Effectively induces cells death in B16 cells	43

The above table describes Poly-ε-caprolactone (PCL) nanoparticle applications for therapeutic needs through insights about drug delivery control and target-specific delivery mechanisms. The Encapsulation Efficiencies (EE) demonstrate a wide spectrum of values, which show flexibility when using the method for various pharmaceutical compounds. PCL nanoparticles provide various benefits to drug delivery, including selective tumor targeting and controlled drug release while preserving the biological activity of insulin and tamoxifen maintenance. Laboratory findings show that PCL nanoparticles accumulate better in cancers and reduce blood sugar levels while allowing drugs to enter cells efficiently, thus demonstrating improved therapeutic delivery and reduced general side effects.

2.4. Chitosan: It is a natural polymer that is modified by chitin by a ratio of 10:1 to 30:1 single choice deacetylation. Different approaches exist for developing chitosan

nanoparticles with ionotropic gelation and microemulsion as well as emulsification solvent diffusion and PEC formation identified among them [44]. This is known as ionotropic gelation and is simply an electrostatic interaction between chitosan's amino group and polyanions (which are destined to precipitate). This is achieved through mechanical stirring between tripolyphosphate and the small-sized nanoparticles, which naturally form using several gelling agents in a continuous feed mode: Ambient conditions were used for the fabrication of chitosan and glutaraldehyde [45,46]. Microemulsion production requires the surfactant to be separated in an organic solvent until the chitosan and glutaraldehyde mixture dissolves in the organic solvent at room temperature under stirring [47]. Self-assembly of cationic chitosan with plasmid DNA at neutral pH, leading to nanoparticle formation upon the addition of the DNA solution to chitosan dissolved in acetic acid, is known as the PEC technique [48]. Enhanced the therapeutic potential for these various drug molecules; their encapsulation was achieved using these different techniques.

2.5. Gelatin: Gelatin is biocompatible, biodegradable, bioactive, and non-toxic; therefore, delivering therapeutics in a sustained-release manner is possible using this material. As a polyampholyte with cationic and anionic groups, swelling and thermal properties are dictated by the applied degree of crosslinking. Thus, gelatin nanoparticles can be prepared through different ways of desolvation/coacervation or emulsions [15,49]. One of the first is the phase separation of a homogeneous solution of charged macromolecules, created by either adding natural salts or alcohols. The use of gelatin nanoparticles exists for medicine encapsulation purposes, which enhances delivery methods and therapeutic effects.

2.6. Poly-alkyl-cyano-acrylates (PAC): Biocompatible poly-alkyl-cyano-acrylates (PAC) undergo degradation by biological enzymes yet produce toxic substances that induce some harm to the central nervous system. For that reason, the application of PACs in humans is prohibited [50]. Generally, making PAC nanoparticles involves either emulsion polymerization, interfacial polymerization, or nanoprecipitation, and emulsion polymerization can use either an organic continuous phase or an aqueous continuous phase. Encapsulation efficiency of drugs of up to 99 % can be achieved through interfacial polymerization, enabling the construction of efficient drug delivery systems [51].

Multiple drug delivery systems use gelatin, chitosan, and poly-alkyl-cyano-acrylates (PAC) nanoparticles in various pharmaceutical applications. The table given below highlights the drug delivery applications of these polymers, which enable precise therapeutic outcomes. Drug delivery systems that use these nanoparticles benefit from their bioactive preservation while delivering improved absorption rates and controlled medication release effects. Therapeutic benefits of these systems involve improved targeted tissue drug retention together with lowered side effects and greater anti-inflammatory potential. Laboratory animal studies indicate three notable outcomes involving treatment of cancer cells while improving drug levels within eyes and enhancing penetration through human skin.

Table 4: Gelatin, Chitosan and Poly-alkyl-cyano-acrylates (PCA) biodegradable nanoparticles for drug delivery

Polymer	Encapsulant	EE	Method of synthesis	Therapeutic Improvement	Release mechanism	In vivo	Reference
Gelatin	Paclitaxel	33–78 %	Desolvation	Biological activity of paclitaxel preserved	Diffusion	Activity against human RTA bladder transitional cancer cells circulation	52
	Didanosine	72.5%	Double desolvation	Slow release up to 24 h	Diffusion	increased brain accumulation of didanosine	53
	Chloroquine phosphate	15–19 %	Solvent evaporation	Reduced side effects	Diffusion	-	54
Chitosan	Cyclosporin A	73 %	Ionic gelation	Therapeutic concentrations achieved in ocular tissues	Dissolution	Higher CyA concentrations in cornea vs.	49

						conjunctiva	
	Ammonium glycyrrhizinate	35 %	Ionic gelation	Enhanced oral absorption	Polymer degradation, Diffusion	-	55
Poly-silyl-cyano-acrylates (PACA)	Ftorafur	-	Anionic polymerization	Controlled release up to 10 h	Diffusion	-	56
	Indomethacin	76.6%	Interfacial polymerization	Increased anti-inflammatory activity after nanoencapsulation	-	Permeated through rat skin within 8 hours	57

3. Advantages of Using Biodegradable Nanoparticles for Sustained Drug Delivery:

Biodegradable nanoparticles have garnered significant interest in drug delivery research because of their unique properties related to biocompatibility, degradability, and tunability. The synthesis of nanoparticles occurs frequently using polymers including PLGA and PLA as well as chitosan, etc. Biodegradable nanoparticles address the problems of drug stability, controlled release, and targeted delivery, thus providing an environmentally friendly and efficient platform for the implementation of therapeutic applications. These few advantages boost and improve patient outcomes and follow environmental principles; therefore, they are an integral part of modern drug delivery research.

3.1. Biocompatibility: Biodegradable nanoparticles reduce toxicity and side effects. Among the most part, polymers such as PLGA, PLA, and chitosan are utilized extensively for drug delivery research because they are biocompatible and have been approved for medicinal use. Therefore, there is safe application of these nanoparticles in various therapeutic scenarios [58].

3.2. Degradability: Biodegradable nanoparticles break down into harmless chemicals under various physiological conditions. These allow a simple means to eliminate the carrier out of the body because of metabolic processes, thereby reducing the chances of retention in the tissues, hence enhancing their overall safety profile [59].

3.3. Efficient Drug Encapsulation: As biodegradable nanoparticles, they can encapsulate small molecules, proteins, peptides, and nucleic acid therapeutic agents that can be delivered to the extracellular and intracellular compartments. Drug encapsulation affords enzymatic protection as well as improving solubility. Encapsulated drugs are retained in the circulatory system for longer periods of time to achieve maximum therapeutic efficacy of these agents to a specific tissue or cell [60].

3.4. Targeted Drug Delivery: The surface of biodegradable nanoparticles receives modification through the attachment of targeting ligands, including antibodies with peptides and aptamers, which will provide them with targeting specificities. This enables them to recognize and bind to certain cells or tissues. The consequence is that targeted delivery not only delivers more therapeutics to the site of action but also away from the sites of action, which will inevitably lead to higher efficacy and safety of the treatment [61].

3.5. Environment Friendliness: Precious tools of sustainable drug delivery are biodegradable nanoparticles that leave no toxic byproducts due to the use of material of natural origin. Additionally, it reduces ecological pollution and follows environmental stewardship. On the other hand, biodegradable is a greener and more sustainable option [58].

3.6. Reduced Waste Generation: Reducing the possibility of nanoparticles accumulating persistently in biological systems or ecosystems is the use of biodegradable materials. Because biodegradable nanoparticles are degraded into metabolizable or excretable byproducts, concern for the environment is alleviated, and extensive waste management techniques are eliminated for nonbiodegradable materials. This additional benefit supports their novelty in changing healthcare practice with sustainability [59].

3.7. Optimized Therapeutic Delivery: The continuous release of drugs from biodegradable nanoparticles, controlled and sustained, prolongs the therapeutic effects and

reduces the frequency of dosages. Optimized delivery such as this would improve patient compliance and decrease systemic toxicity. These biodegradable nanoparticles enhance the therapeutic indices of encapsulated agents, such as efficacy and sustainable healthcare solutions, have been enabled [62].

4. Computational Modeling in Nanoparticle Design:

Nanoparticle behavior within biological systems can be predicted through powerful computational approaches of molecular dynamics simulation and molecular docking. The combination of these methods allows investigation of interactions at the atomic level and suggests the ways in which nanoparticles interact with cellular components.

4.1. Molecular Docking: In this approach, the small molecules, like drugs, predict the binding of their target proteins. The method utilizes a simulated binding process of the ligand to the protein. These modes of ligand binding may serve in guiding the design of more effective nanoparticles for drug delivery. Major software for docking purposes includes AutoDock and GOLD, which allow rapid screening for large compound libraries [63].

4.2. Molecular Dynamics Simulations: Molecular dynamics simulations afford a time-dependent dynamic view that helps in studying how nanoparticles behave in a biological environment. For example, modes of binding determine the stability of the nanoparticle-protein complexes under heap physiological conditions [64]. This combination of docking and MD simulations will work to develop a basic understanding of nanoparticle behavior to optimize their design for drug delivery applications.

4.3. Drug-Loading and Release Mechanisms: Efficient loading of drugs and controlled release are critical parameters in designing effective nanoparticle systems for drug delivery. The high loading capacity minimizes the amount of carrier material needed for administration, thus enhancing therapeutic efficacy while minimizing side effects. The drug loading into nanoparticles can be accomplished in two main ways: incorporation of the drug either during the NP production stage or adsorption of the drug onto a formation of NPs by incubating them within the drug solution [39]. These approaches permit a variety of interactions, depending on the nature of the polymer matrix encapsulation, dispersion within the polymer, adsorption on the surface, or chemical binding to the polymer. The efficiency of these interactions is determined by the physicochemical properties of both the drug and polymer and the loading conditions of the drug [38].
The determination of drug-polymer interactions and loading efficiency is analyzed using adsorption isotherms. Linear sorption isotherms characterize solid solutions while Langmuir describes surface adsorption phenomena. Such isotherms thus give important insights into the binding dynamics and the suitability of the formulation for drug delivery.

Accurate determination of the drug loading capacity often requires safe and reliable separation techniques such as ultracentrifugation or gel filtration that can separate nanoparticles from unbound drug molecules. The encapsulation efficiency (EE) is then measured by the given formula:

EE = (Total amount of drug used for formulation/Total mass of formulation) X 100

Simultaneously, understanding the mechanisms underlying drug release is necessary, as is the development of sustained-release formulations. Drug release happens from nanoparticles through several mechanisms, including desorption of surface-bound drug and diffusion through the nanoparticle matrix and diffusion across the polymeric wall of nanocapsules, together with erosion of the nanoparticle matrix and a combination of erosion alongside diffusion processes. The release kinetics can be modeled using the biexponential function:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

Where C is the drug concentration remaining in nanoparticles at time t, A and B are constants representing diffusion- and erosion-controlled systems, respectively, and α and β are rate constants derived from semilogarithmic plots [65].

The release of the drug is affected by several factors, like drug solubility and diffusion properties and the rate of biodegradability of the polymer matrix. By and large, compared to small nanoparticles, bulkier nanoparticles are thought to produce lower initial burst release due to their greater surface area-to-volume ratio. In contrast, the drug loading amount has been reported to be directly proportional to both burst and sustained drug release. In systems where the drug can diffuse out of the nanospheres, release is generally through diffusion or erosion under sustained sink conditions. Burst release often arises from weakly bound or surface-adsorbed drugs [66, 67].
The polymer choice plays an important role in the modulation of drug release profiles.

5. Real-World Examples of Computationally Guided Nanoparticle Development:

For a range of biomedical applications, the development of nanoparticles has been guided by computational tools. Notable examples include:

5.1. High-Throughput Screening: A study combined high-throughput experimentation and machine learning to discover drug nanoparticles that self-assemble from millions of combinations. The computational tools used in this method identified novel formulations that they showed had high drug loading capacity, effectively proving how computational tools can dramatically expedite the process of nanoparticle development [68].

5.2. Nanoparticle-Mediated Hyperthermia: Magnetic and gold nanoparticles optimized for hyperthermia cancer therapy have been computed. Through the simulation of several excitation wavelengths and nanoparticle properties, the researchers could maximize therapeutic efficacy while minimizing side effects [69]. These models make predictions about the in vivo performance of nanoparticles and guide their design for clinical purposes.
5.3. Nano-bio interface interactions: Insights have been obtained from simulation work concerning the interaction of nanoparticles with cell membranes. The work of this sort is critical in unpacking biodistribution and cellular uptake systems. Applications to study dynamic processes, for instance, endocytosis, also provide insights into dynamic aspects of effective drug delivery systems [70].

5.4. mRNA-Loaded Lipid Nanoparticles (LNPs): Computation-based models led to the optimal development of LNPs that transported mRNA vaccines, including COVID-19 vaccines, by tuning lipid content and PEG modifications. Modeling showed that endosomal escape along with mRNA protection ensured more than a 95% success rate of delivery throughout in vivo testing. The developed work became the basis for creating FDA-approved LNPs [71].

5.5. Targeted Neurodegenerative Therapy: Apolipoprotein E ligands were applied to silica nanoparticles through computational design to help these nanoparticles effectively pass the blood-brain barrier (BBB). Designer nanoscale particles were synthesized using ligand-receptor binding simulation data, which led to 4× better brain accumulation rates in Alzheimer's disease mouse models than untargeted nanostructures [72].

5.6. Photodynamic Therapy (PDT) Nanosystems: The process of optimizing gold nanoparticle-porphyrin photosensitizers was conducted through quantum mechanical computation. The ROS yield efficiency of light-triggered reactive oxygen species generation simulations reached 80% for nanoparticles, which allowed accurate tumour treatment through PDT [73].

6. Sustainability Challenges and Solutions:

6.1. Addressing scale-up challenges for biodegradable materials: The use of biodegradable polymers to produce environment-friendly nanoparticles for controlled drug delivery on a large scale has some drawbacks, especially in the quality and efficiency of the nanoparticles during the production process. Many scientists recognize biodegradable polymeric nanoparticles (BPNPs) for their significant drug delivery capabilities owing to their biocompatibility, degradability, and drug stability and bioavailability improvement properties. However, bringing these materials to a mass level requires issues like repeatability of the process, cost, and legal parameters to be considered. The following sections elaborate on these challenges as follows;

6.1.1. Production Consistency and Quality Control: Stability under physiological conditions is critical to the guaranteeing therapeutic efficacy of nanocarriers, particularly when upscaling the production. It includes not only the precise control of the synthesis conditions to exhibit the suitable size and composition but also the surface modification for increasing biocompatibility and preventing nanoparticle aggregation. pH, ionic strength, and ability to bind with serum proteins have a destabilizing effect on nanoparticles; hence, the need to closely model physiological conditions during in vitro and in vivo tests [74]. One of the most relevant fields that can be used as a solution for the efficient synthesis of the nanoparticles is a green synthesis. The incorporation of plant extracts or other biological components not only reduces the environmental effects but also introduces additives such as bioactive compounds, which increase the functionality of the nanoparticles. For example, the active compounds in plant extracts can simultaneously reduce and stabilize the formation of nanoparticles, which are far less toxic than other comparable nanoparticles in the treatment of diseases. Also, green synthesis methods can be easily scaled up and are much cheaper than other synthesis methods for use in industries without violating environmental policies [75].

6.1.2. Cost-Effectiveness and Economic Viability: Biopolymers and bio-based nanoparticles for sustainable biomaterials also prove to have strong economic benefits. Natural abundance of such materials decreases demand for synthetic precursors with costly prices. Also, they do not require much energy to be mined and synthesized, which is a cost-saving factor [76]. Green nanotechnology is sustainability integrated with economic competency. The practices of green nanotechnology involve non-toxic solvents, renewable energy, and low temperature, and these measures lower the expenses of operation. In addition, the production of limited dangerous by-products and wastes reduces costs connected with waste disposal and conformity with ecological rules. Similarly, the integration of green principles into nanoparticle synthesis procedures can enhance the degree of scalability of these methods, which makes many of them very competitive for large-scale implementation, while maintaining their high effectiveness [78,79].

6.1.3. Regulatory and Commercialization Challenges: The use of sustainable biomaterials in pharmaceutical applications comes with unique challenges regarding its regulatory compliance. The manufacturers and developers need to ensure the safety, biocompatibility, and overall therapeutic effectiveness of these materials to stringent regulatory requirements. This includes cytotoxicity tests, immunogenicity tests, and determination of long-term stability of such formulations. Further, the regulatory agencies insist on the compilation of records showing the source of biomaterials, methods used to synthesize, and steps taken to control the variability of results [76]. Therefore, for the biomaterials to be commercialized, they must be scalable in terms of production that will

meet the set regulations and laws. Similarly, for large scale manufacturing, it is necessary to preserve such properties as biocompatibility and therapeutic activity of these materials. This has envisioned the need to arrive at well-defined synthesis protocols that can be easily replicated. Moreover, price control is considered essential, especially at a time when costs must be adjusted sharply downwards in many industries. Continuous manufacturing systems as well as automation of the quality control system are some improvements in the production technologies that can respond to this challenge efficiently and cheaply without undermining the regulatory requirements [76]. Biodegradable materials are considered to have enormous possibilities for creating long-term drug delivery systems; however, the difficulties in increasing production must not be overlooked. To overcome these challenges, a cross-sectoral approach should be applied by means of improvements in green chemistry, material science, and regulation to pave the way for a successful transition and implementation of the eco-friendly nanoparticles' application in healthcare.

6.2. Enhancing cost-effectiveness of production methods: The synthesis of environment-friendly nanoparticles for efficient and green drug delivery further improves the affordability of production techniques. The green synthesis of nanoparticles avoids hazardous materials and cuts costs compared to standard methods while retaining their effectiveness in a drug delivery system. This approach utilizes a renewable resource, plant extracts, to synthesize non-toxic and efficient nanoparticles.

6.2.1. Green Synthesis Techniques: Plant-mediated synthesis utilizes the natural reductants and stabilizers available with the plant extracts. This method also reduces the amount of lethal chemicals and enables size and phenomenon uniformity due to the controlled reduction process of using plant bioactive. This environmentally sustainable and economic process is most beneficial for high-volume output since it does not consume energy and generates waste [80,81]. Nanoparticles obtained from renewable polymers containing chitosan, cellulose, and alginate are widely used due to their biodegradable and biocompatible nature. People find its drug delivery system applications valuable because the method allows therapeutic agents to be encapsulated for absolute release control. Also, the raw materials are renewable, and the processes are easy and cost-effective to perform, which implies an economic and, therefore, environmental sustainability of these materials for use in pharmaceutical and biomedical purposes [82]. Green chemistry recognizes and replaces the hazardous substances in a process, and this will reduce the overall cost of production. Vegetable oil and products from biomass are found to be a cleaner source of materials for use in place of materials derived from petroleum, also bringing about lesser costs [78, 83].

6.3. Integration of computational approaches for greener solutions: The incorporation of computational methods in designing environmentally friendly nanoparticles for sustained drug delivery is an exciting subject synthesizing green chemistry and modern

nanotechnology. This combination fosters improvement in the effectiveness of carriers for drug delivery systems and the reduction of environmental pollution. The following sections present the different features of this integration:

6.3.1. Role of Computational Modeling: The application of various computational modeling approaches, like molecular dynamics simulations and pharmacokinetic modeling, is crucial for the best design of nanoparticles and efficient drug encapsulation. These models allow the fine description of nanoparticle behavior and its effects on biological membranes, drugs that are enclosed in nanoparticles, or the fluids that those nanoparticles are surrounded with. Through experimental control of parameters such as size, geometry, and charge, it is possible to fine-tune nanoparticle characteristics to improve function. The ADME properties of drug matters in nanoparticles, together with kinematic modeling, help researchers establish pharmacological benefits and reduce treatment complications in preclinical trials [84,85]. Besides optimization, computational models have the ability to yield mechanistic information about the molecular behavior between nanoparticles and biological systems or therapeutic compounds. These models explain binding affinities, cellular receptor binding profile, and drug release profiles, which are essential for making targeted and efficient drug delivery systems. This mechanistic view enhances the progress of top-notch drug delivery systems while reducing their costs and the time required to develop them [86].

6.3.2. Future Prospects: The combination of green nanoparticles into the concept of personalized therapy is a promising one in the development of efficient and environmentally friendly medicine. If green nanoparticle technology is integrated with the conventional medical systems such as Ayurveda, then the treatments could be developed for each patient, and they are eco-friendly as well [87,88].

The elimination of the use of toxic agents, cutting down on waste, and optimizing energy utilization in the synthesis contribute to environmental conservation and increase the safety of drugs [89].

However, apart from these achievements, there are still some issues that need to be addressed before these technologies could be used in large-scale clinical practice. Purity, quality control, regulatory issues, and cost factors are among some of the concerns that deserve an exceptional focus during scale-up.

7. Conclusion:

The use of biodegradable nanoparticles in drug delivery could solve many problems of contemporary medicine while being at the same time fundamentally environmentally safe and biocompatible. A synergy of computation and green synthesis approaches has greatly enhanced the formulation and delivery of such platforms for targeted drug delivery with minimal ecological footprint and reduced toxicity. By systems based on bioactive

compounds from nature, such systems realize the principles of personalized medicine, making the therapies adapted to each patient's individual needs. Green nanotechnology's convergence with standard Ayurveda medical systems further emphasizes its ability to harmonize old traditional healing knowledge with the latest kind of innovation to give up culturally relevant and sustainable healthcare. Despite these promising developments, several challenges impede the widespread clinical translation of green nanoparticles. A key barrier is to obtain high purity, tight quality control, scalable manufacturing, regulatory compliance, and cost-effectiveness. These issues must be addressed to satisfy global health needs and UN Sustainable Development Goals (UNSDGs) objectives, which include promoting environmental conservation and equitable access to healthcare as well as responsible use of resources. However, large-scale applications in industrial processes pose other problems that need to be overcome before large-scale production can be achieved. In upcoming work, research should advance green manufacturing processes and employ computational techniques for the optimization of biodegradable nanoparticles in a broad context. All these advances offer great possibilities for changing the situation with healthcare services provision as well as for enhancing environmental friendliness all across the world.

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