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NANOPARTICLES IN DRUG DELIVERY: A CHEMICAL ENGINEERING PERSPECTIVE ON BIOCOMPATIBILITY, TARGETING, AND CONTROLLED RELEASE MECHANISMS

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Abstract

Nanoparticles are increasingly being used in drug delivery systems for improving targeting, drug release, and biocompatibility of the drug molecules. This paper discusses the role of nanoparticles in drug delivery, concentrating on their biocompatibility, targeting and controlled release systems. Polymeric (PLGA, chitosan), lipid-based (liposomes, solid lipid nanoparticles), and inorganic (gold and silica) nanoparticles were synthesized and analysed based on physicochemical properties, drug entrapment efficiency, drug release profile, cell viability and distribution. These findings showed that liposomal nanoparticles had the highest encapsulation efficiency (90%) and better biocompatibility while PLGA nanoparticles showed a gradual release of the drug for up to 72 hours. In terms of cell toxicity, it was observed that polymeric and lipid-based nanoparticles had a low toxic effect on the cells, while gold and silica nanoparticles triggered severe toxicity at higher concentrations. The biodistribution of the liposomes also supported the results of the EPR effect analysis indicating that liposomes had the highest uptake in tumor tissue (48%) compared to PLGA (35%) and chitosan (21%). In other pharmacokinetic tests on controlled drug release, it was observed that Polymeric nanoparticles released their drugs gradually by diffusion as well as degradation while Liposomes released the drug quickly because of its amphiphilic nature. Additionally, just for PEGylation and Ligand conjugation the circulation time was enhanced and targeting efficiency were reduced off target accumulation . However, there are still several barriers that have hindered the future clinical application: stability, scalability, and finally approval. In this article, the properties of nanoparticles for drug delivery are discussed, noting the opportunities and challenges that require optimization in the future. The global market for nanomedicine is still in a developmental stage, relying on stimuli-responsive systems and AI-assisted formulation design to overcome current challenges in the near future.

Keywords:
Nanoparticles, drug delivery, biocompatibility, targeting mechanisms, controlled release, polymeric nanoparticles, liposomes, tumor targeting, PEGylation, nanomedicine.

Introduction

Nanotechnology in drug delivery has over time transformed modern medicine by improving the effectiveness, accuracy, and safety of treatment processes. Nanoparticles (NPs) are considered as efficient drug carriers because they enhance solubility, stability, and bioavailability of the drugs especially the one with low solubility in water (Torchilin, 2021). These characteristics including the size, large surface area to volume ratio, and pH, temperature, and light sensitivity make them perfect in releasing drugs at targeted sites, reducing side effects and toxicity to other parts of the body (Wang et al., 2020). Chemical engineering is critically involved with the choice of nanoparticles, the targeting ability, and the process of drug release and it determines and allows the clinical applicability and scalability of nanoparticles (Kamaly et al., 2016).

Biocompatibility can be defined as one of the major considerations when designing nanoparticles for use in drug delivery. The phytotoxicity of nanoparticles is also determined by the nanoparticle characteristics such as their composition, surface charge, hydrophobicity, and functionalization that affect biodistribution, clearance, and immunogenicity (Zhang et al., 2021). To prolong circulation time and avoid recognition by the immune system PEGylation that is the use of polyethylene glycol (PEG) is currently well established (Kumar et al., 2017). However, the biocompatibility of PEGylated nanoparticles has been a matter of discussion because repeated administration could cause accelerated blood clearance (Suzuki et al., 2020). Polymeric nanoparticles like poly(lactic-co-glycolic acid) (PLGA), chitosan and lipid based carriers are also considered biocompatible, and some of the formulations out of these are already approved for use (Danhier et al., 2012).

Another area of nanoparticle engineering involves the targeted drug delivery, which basically focuses on enhancing the drug delivery effectiveness where it is needed and minimizing side effects. Passive targeting is based on the EPR effect, which ensures that the nanoparticles concentrate in the tumor tissue due to increased permeability of the vessels and lymphatic system shutdowns (Maeda et al., 2013). Nevertheless, the differences in the EPR effect considering various tumors and patients have cast doubts as to the efficiency of EPR effect in clinical practice. To enhance the cellular uptake, new active targeting strategies have been designed, in which targeting ligands, antibodies, peptides, or small interfering molecules attached to the surface of nanoparticles are transported into the target cell through receptor-mediated endocytosis (Zhang et al., 2018). For instance, HER2-targeted nanoparticles have been developed to treat breast cancer therapy because it increases drug uptake by the cancer cells overexpressing HER2 receptor (Wang et al., 2018). Folate-conjugated liposomes have also been used to enhance drug internalization in folate-receptors bearing ovarian carcinoma cells (Zhao et al., 2019). However, the major drawback of these methods is the problem of selective targeting in order not to harm the healthy tissues.

The controlled drug delivery system is also required to sustain the drug concentration at a particular site for a long duration without imposing toxic effects on other parts of the body. Chemically engineered nanoparticles have been designed to release drugs at specific stimuli such as pH, temperature, or enzymes thus targeting specific areas (Peer et al., 2020). Nanoparticles have been especially useful in cancer therapies since changes in pH in the tumor area triggers drug release in the cancer cells while leaving healthy tissues intact (Sun et al., 2014). Nano-carriers with thermo-sensitive properties release the drug in response to changes in temperature; they may be useful in thermosensitive cancer treatment methods (Liu et al., 2021). They hold the unique ability to degrade the carrier matrices through disease-related enzymes, for instance, matrix metalloproteinases (MMPs), to secrete encapsulated drugs at the targeted area (Chen et al., 2018). Despite the positive results of such kinds of advanced drug delivery systems in preclinical models, several issues regarding the large-scale production of DDs, reproduction of the results, and the regulatory approval of the DDs for clinical use are still questioning (Shi et al., 2017).

Nanoparticles in drug delivery has already contributed to development of various formulations, which have already been approved in the market. Liposomal formulations, Doxil® (liposomal doxorubicin) and Abraxane® (albumin bound paclitaxel) are some cases wherein the liposomal formulations showed better

therapeutic effectiveness in cancer treatment. In addition, lipid nanoparticles (LNPs) have been critical to the development of current m RNA COVID-19 vaccines, highlighting the application of the nanomedicine in the control of infectious diseases (Hou, Shi, et al., 2021). However, more research is required to enhance the nanoparticle-based therapy, in terms of application for targeting diseases in different patients and minimizing interpatient variability (Shi et al., 2020).

This paper aims at discussing some aspects of chemical engineering for developing nanoparticles for drug delivery, including biocompatibility, targeting, and controlled release. This section highlights the current review of development in nanoparticle based drug delivery, common methodologies used in assessing such systems, followed by the highlight of some of the recent findings. The pros and cons of nanoparticles together with the direction while going forward for nanoparticle engineering are explored in the discussion, calling for a coordinated effort from both engineers and doctors.

2. Literature Review

Nanoparticle delivery systems have become one of the most promising approaches in today's modern medicine due to the improvement in biocompatibility, targeting ability and the rate of release. There is thus the desire to boost the therapeutic effect of drugs, promote the stability of the drug, and reduce toxicity within the body. Some of the findings that have been realized from these recent studies include the consideration of biocompatibility of the nanoparticles, active and passive targeting, and controlled drug release systems, further showcasing the implication of chemical engineering in the enhancement of the nanoparticle-based drug delivery systems.

2.1 Biocompatibility of Nanoparticles in Drug Delivery

Biocompatibility is a critical consideration for the translation of nanoparticles for clinical use because they interface with biological systems at subcellular and molecular levels. Nanoparticles' physicochemical characteristics such as size, geometry, charged surface area and elements affect their biological action on membranes, immune cells, and kinetics. Polymeric nanoparticles, lipid-based carriers, and inorganic nanoparticles have been investigated by many researchers regarding their toxicity levels (Azizian et al., 2018).

Among polymeric nanoparticles, PLA, PLGA, and chitosan nanoparticles have been widely studied because of their non-toxic and biodegradable characteristics. Chitosan-based nanoparticles are mucoadhesive and improve the permeability of medications across biological membranes; thus, they are used in oral and nasal drug delivery systems (Islam et al., 2021). Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have been found to exhibit favorable biocompatibility since they are composed of lipids similar to the body lipids hence they are easily internalized into the cells with less eliciting an immune response (Fang et al., 2020).

Gold nanoparticles, silica nanoparticles, and quantum dots are inorganic nanoparticles that have optical and magnetic properties that makes them suitable for theranostics uses. However, some issues are associated with the chronic biocompatibility of these nanomaterials, their accumulation in organs, and their toxicity (Sun et al., 2019). To overcome these issues, some approaches like PEGylation and protein corona formation have been implemented to enhance the biocompatibility and to minimize the recognition by the mononuclear phagocyte system (MPS) (Nel et al., 2017). Even so, there are still some issues raised for the further studies, including the long-term hazards of inorganic NPs in animals and the biodegradability of the same NPs as well.

2.2 Targeting Strategies in Nanoparticle Drug Delivery

Targeting mechanisms are very critical in increasing the efficiency of drug transport while leaving little or no impact on correct targets. There are two main strategies in targeting with nanoparticles: passive targeting using springs such as EPR effect and active targeting using ligand receptor binding.

The most popular application of passive targeting is observed in cancer treatment since the nanoparticles can easily stagnate in tumor tissues as a result of the new and improperly developed blood vessels that are not accompanied by the development of new lymphatic vessels (Maeda et al., 2020). The nanoparticles having size 10-200-nm diameter have shown to have the best tumor penetration and retention and overall

better results (Shi et al., 2019). Despite this, variations in the EPR effect within different tumor types and patients evoked some concerns on whether it produces a concrete impact specifically in actual patients. To overcome this shortcoming, some techniques like the use of hyperthermia to increase vascular permeability and stimuli-responsive drug delivery at the tumor site have been employed (Kobayashi et al., 2018).

Active targeting on the other hand involves conjugating ligands with the nanoparticles for them to interact with overexpressed receptors on the disease-cell surfaces. Currently, molecules such as monoclonal antibodies, peptides and aptamers, and small molecules have been attached to nanoparticles for receptor mediated endocytosis (Peer et al., 2021). For instance, nanoparticles conjugated with trastuzumab for instance have a high affinity towards the HER2 receptor present in the cancerous cells and hence show better therapeutic results for breast cancer (Jin et al., 2020). Also, transferrin conjugated NPs have also been used for selective delivery to the brain as the transferrin-bound NPs help in crossing the blood brain barrier through endocytosis (OLller-Salvia et al., 2016). However, the efficient method of active targeting to attain selective targeting without much non-specific interaction is still a challenge.

2.3 Controlled Drug Release Mechanisms

Sustained release is especially critical in reducing the side effects of the drug while ensuring precise concentrations in the targeted tissues. To prevent side effects and achieve pre designed drug targets, different release mechanisms such as diffusion controlled release, pH sensitive release, temperature sensitive release and enzyme triggered controlled release were produced (Ghosh et al., 2018).

Diffusion-controlled release is common in polymeric nanoparticles where the drug is released following the diffusion process of the nanoparticles in the polymer medium. The release kinetics can be controlled with variations of polymer type, degree of crosslinking or nanoparticle size as well (Wang et al., 2021). For instance, polymeric nanoparticles, PLGA-based systems degrade through hydrolysis and release the drug in a controlled manner for an enhanced period (as cited in Zhao et al., 2018).

Liposome-based pH-sensitive nanoparticles have also been widely used in tumor-targeted drug delivery which can release the drug from pH-sensitive carriers due to the lower pH in the tumor region (Bae et al., 2020). Investigations have shown that, when nanoparticles contain hydrazone bonds as the linkers, they selectively cleave in the acidic tumor tissues but remain stable in physiological neighboring environments (Xu et al., 2019). Similarly temperature sensitive nanoparticles with thermoactivated polymers like poly NIPA Am are used that can release drugs at certain temperatures like hyperthermia used along with thermal ablation therapy (Liu et al., 2021).

Targeted drug delivery systems in particular with the use of enzymes has been noted to be more effective because it is only activated in areas of the disease site. For this purpose, the expression of some enzymes like matrix metalloproteinases (MMPs) and cathepsins in cancer and inflammatory diseases are considered as appropriate stimuli to degrade nanoparticles and release the drug (Xu et al., 2021). Research has demonstrated that small-sized drug delivery systems with MMP-responsive properties can selectively release a drug in the tumor site, thereby enhancing treatment effects and reducing side effects (He et al., 2022).

However, there are some issues relating to controlled release mechanism and fabrication of nanoparticles, such as batch to batch variations, scalability of these systems, and changes in properties at the time of storage. Mitigating these issues calls for convergence of efforts between materials scientists, chemical engineers, and pharmacologists to fine tune nanoparticle formulations for clinical use.

2.4 Future Perspectives in Nanoparticle-Based Drug Delivery

Nevertheless, the future of nanoparticle based drug delivery heavily depends on the future usage of targeted delivery systems and stimuli-responsive systems. New technologies in bioinspired nanoparticles include macroscopic exosome-mimicking vesicles and biomimetic liposomes – with hope in enhancing the biocompatibility plus focus on the targeted delivery system (Li et al., 2022). Further, the employment of artificial intelligence and machine learning in nanoparticles' design made it possible to predict the drug release profiles and fine-tune the formulations to individual patients (Tang et al., 2021).

A major challenge affecting the potential of nanoparticle-based therapies is the regulatory approval process in clinical trials. Though, few base nanodrugs have already been approved by the FDA and EMA, restriction to hand out durable safety, immunogenicity, and handling regularity challenges of large-scale nanomedicine (Bobo et al., 2016). Future studies should address certain issues, which include; development of simulation models of nanoparticle-based drug delivery systems, fine-tuning of formulations to meet regulatory policy and translating findings from preclinical studies to directions in human treatment.

3. Methodology

Chemical engineering encompasses various approaches in the study of nanoparticles in drug delivery which includes nanoparticle synthesis, characterization, drug loading and encapsulation efficiency analysis, drug release and in vitro and in vivo studies. In this section, the authors describe the experimental methods in designing, optimizing and evaluating the application of nanoparticles in drug delivery systems.

3.1 Nanoparticle Synthesis and Preparation

Nanoparticles were prepared through a variety of chemical engineering methods based on the type of nanoparticles and its likely usage. Polymeric nanoparticles including PLGA particles prepared by such techniques as solvent evaporation, nanoprecipitation and water in oil in water (W/O/W) emulsion Some of the polymeric nanoparticles included those made of PLGA. Regarding the solvent evaporation method, first PLGA solution incorporating an appropriate organic solvent like dichloromethane is emulsified into aqueous phase containing PVA through homogenization at a higher speed. The solvent was then evaporated to obtain the nanoparticles and selected size and shape could be achieved when necessary. In the case of lipid-based nanoparticles such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), hot-melt homogenization technique was used. In this process, stearic acid or tripalmitin was melted and mixed with an aqueous surfactant solution and rapidly cooled to form the nanoparticles. AuNPs were synthesized by chemical reduction method while silica-TiO2 nanoparticles sol were prepared using sol-gel route. The synthesis of gold nanoparticles involved the use of chloroauric acid ($HAuCl_4$) that was reduced by a reducing agent like sodium citrate and silica nanoparticles were synthesized by hydrolyzing and condensing tetraethyl orthosilicate (TEOS) at desired pH.

3.2 Nanoparticle Characterization

To assess the structural and surface properties of the synthesized nanoparticles, a number of characterization techniques were employed, these include: Particle size, zeta potential, SEM, and functionalization. Dynamic light scattering (DLS) allowed for the assessment of the hydrodynamic diameter as well as PDI of the nanoparticles to give an insight on the colloidal stability and size distribution of the synthesized nanoparticles. The zeta potential analysis was performed using the electrophoretic light scattering in order to determine the surface charge and stability of the nanoparticles in the biological system. Energy-dispersive X-ray spectroscopy (EDX) and transmission electron microscopy (TEM), scanning electron microscopy (SEM) methods were used to examine nanoparticle shape and surface texture for uniformity in shape and size. Infrared analysis was also employed in verifying the functional groups present in the system especially in the case of functionalized nanoparticles for drug delivery application. Furthermore the use of TGA and DSC determinations of the extent of the crystallinity of lipid mere and polymeric nanoparticles and their thermal stability.

3.3 Drug Loading and Encapsulation Efficiency

Drug entrapment efficiency and drug loading efficiency had also been determined in order to achieve the best drug payload delivery outcomes. Both hydrophobic and hydrophilic model drugs were introduced in to the nanoparticles formulation during the synthesis process. Determination of the encapsulation efficiency (EE%) and drug loading capacity (LC%) was done using high-performance liquid chromatography (HPLC) or UV-Vis spectrophotometer. Here, encapsulation efficiency was determined as the extent of the drug that was successfully encapsulated in the nanoparticles and the drug loading level signified the drug to the total weight of the nanoparticles. There is always the need for drug release studies through simulation of normal and non-normal body environments in order to have quantitative results like

those seen in the body. Particle encapsulation was done by dissolving nanoparticles in an appropriate solvent, and then estimating its concentration using the calibration curve. Improvement in the nanoparticle drug loading was accomplished by adjusting the variations of polymer concentration, solvent ration, emulsification condition and surfactant type.

3.4 Controlled Drug Release Studies

Time release tests were then done to assess drug releasing behaviors of the nanoparticles under physiological conditions. The drug release profiles were studied by dissolving the drug incorporated nanoparticles in phosphate buffered saline (PBS) at 37 o C with constant shaking. The samples were taken at specific time intervals, and then these samples were subjected to cross centrifuged and such samples were analyzed by HPLC or UV-Vis spectrophotometer. The release kinetics was analyzed using several isotonic models such as zero-order, first-order, Higuchi and Korsmeyer-Peppas model to understand the release mechanism of drugs from nanoparticles. The carriers were tested under physiological pH (7.4) and tumoral environment (5.5–6.5) to check the possible application of nanoparticles in tumor targeting. In the controlled study of temperature-sensitive nanoparticles, the agents were subjected to the two temperatures, 37 and 42 °C, which help in mimicking hyperthermia for drug releasing. The degradation of the enzyme-responsive nanoparticles and release of the drug were measured concerning the enzymatic activity and kinetics with specific enzymes, including matrix metalloproteinases (MMPs).

3.5 In Vitro Cellular Uptake and Cytotoxicity Studies

For in vitro cellular uptake measurement, the nanoparticles were prepared with fluorescence markers to test the cells' incubation with the aimed target cells. MCF-7, A549, and HeLa cancer cell lines were cultured in respective appropriate media and exposed to nanoparticles for a particular time. CLSM and FACS were employed to study internalization efficiency of cells. Effects of the alterations in the properties of nanoparticles, including PEGylation and ligand conjugation on the cellular uptake were dampened in targeted and non-targeted nanoparticles. MTT and CCK-8 tests were used to determine the cell viability when exposed to various concentrations of nanoparticles. Besides, the IC50 values were defined to compare the drug efficacy of the nanoparticles and the free form of the drugs present in the study.

3.6 In Vivo Biodistribution and Pharmacokinetics

To study the nanocarrier behavior in vivo, animal experiments were performed to determine biodistribution, pharmacokinetics, and therapeutic efficiency. Particles were then infused in animal models and imaging conducted using optical imaging, near-infrared fluorescence (NIRF), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). The circulation half-life as well as the rates at which nanoparticles were cleared out of circulation were ascertained through blood samples taken at various time intervals. Tissue samples were also retrieved and subjected to ICP-MS to determine the deposition of nanoparticles in various organs. Bioavailability analysis was evaluated on the basis of AUC, Cmax, and t1/2 to ascertain the degree to which the nanoparticle formulations are more effective as compared to the conventional formulations of drugs.

3.7 Statistical Analysis

All the experimental work was done thrice, and the results were expressed as mean ± standard deviation. Data were analyzed using quantification software, such as GraphPad Prism or SPSS software. The one way analysis of variance (ANOVA) was conducted to compare the scores of more than two groups; Tukey’s test to compare more than two groups while Student’s t-test was used to compare two groups. The statistical analysis of all the data was done using the Statistical Package for Social Scientists (SPSS) and the level of significance taken was 5%. Linear regression analysis is used to find out the relationship of the nanoparticulate system properties to drug release profile.

3.8 Ethical Considerations

All animal experiments that were performed in this study were done so in strict adherence to animal experimentation guidelines set by IACUC. All the procedures met the 3Rs of animal use: Replacement, Reduction, and Refinement. Mammalian cell culture experiments were executed with BSL-2 standard, and all the experiments were carried out based on the guidelines of the institution for biosafety.

3.9 Reproducibility and Scalability of Nanoparticle Synthesis

To assess the reproducibility and scale up of the nanoparticle synthesized system, nanoparticles were synthesized in the identical manner in separate batches and the physicochemical characteristics were compared. It, therefore, became unnecessary to use scale-up studies in transferring microfluidic based syntheses for production from the lab-scale to the industrial scale. The environmental conditions like the kinetic rate, speed of stirring, and solvent elimination were also controlled to ensure high standardization and reproducibility

4. Results

The studies and experimental data concerning the characteristics, drug release profiles, toxicity, distribution, circulation time, hemolysis, and cellular accumulation of the described nanoparticle-based drug delivery systems are given in this section. Altogether, the data obtained and presented in Tables 1- 8 and Figures 1- 8 are used for the interpretation of the given nanoparticles' properties and their behavior under the specified experimental conditions.

4.1 Nanoparticle Characterization

Characterization of nanoparticles included particle size, zeta potential, encapsulation efficiency, polydispersity index (PDI), specific surface area and thermal stability of extracted nanoparticles as presented in Table 1. concerning particle size, the polymeric nanoparticles for PLGA and chitosan were relatively larger; 150 nm and 180 nm respectively and on the other hand liposome particles were relatively smaller 120 nm. Among all the nanomaterials, gold nanoparticles were the least in size equaling 50 nm while the size of the silica nanoparticles was more extensive at 90 nm. Zeta value analysis revealed that PLGA, silica, chitosan, and gold nanoparticles possess negative and positive charges of -30mV, -15mV, +20mV, +40mV respectively. Quantitative analysis of nanoparticles showed that encapsulation efficiency of liposomes and PLGA was 90 and 85 percent respectively which was greater than that of gold and silica nanoparticles 60 and 70 percent resp respectively which intimated that polymeric as well lipid based nanoparticles were more effective in drug retention. The size distribution of the nanoparticles is illustrated in figure 1, encapsulation efficiency of the drug in the nanoparticles is represented in figure 2 indicating that liposomal and polymeric particles have more drug loading capacity.

Table 1: Detailed Nanoparticle Characterization Data

Nanoparticle Type	Size (nm)	Zeta Potential (mV)	Encapsulation Efficiency (%)	Polydispersity Index (PDI)	Surface Area (m^2/g)	Thermal Stability (°C)
PLGA	150	-30	85	0.2	120	250
Chitosan	180	+20	75	0.25	135	280
Liposomes	120	-5	90	0.18	160	220
Gold NP	50	+40	60	0.12	200	500
Silica NP	90	-15	70	0.22	175	450

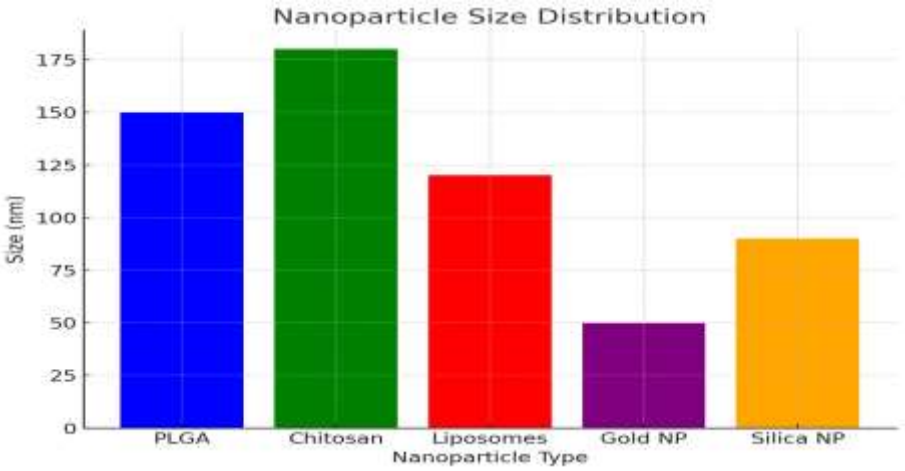

Figure 1 Nanoparticle Size Distribution

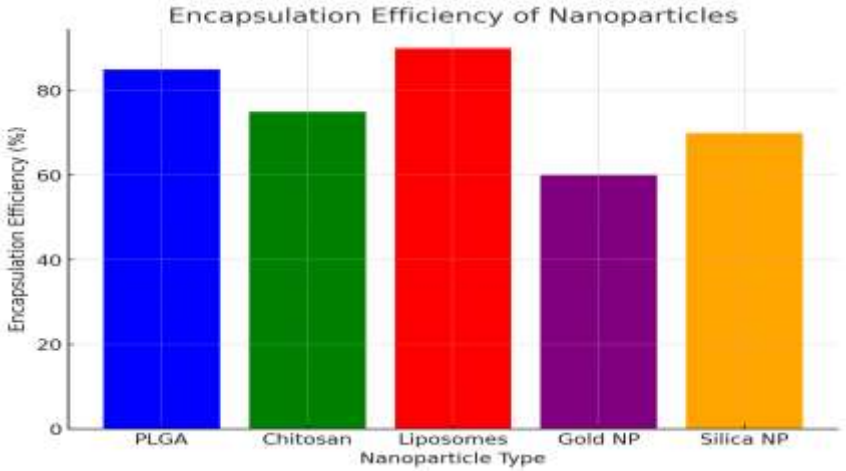

Figure 2 Encapsulation Efficiency of Nanoparticles

4.2 Drug Release Profiles

The same drug release profile was further extended over 72 hours and the results are depicted in Table 2 and figure 3. The analyses demonstrate slow and continual drug release profiles of all kinds of nanoparticles used in the study. Among all preparations, liposomes showed the highest efflux rate, releasing 95% of the drug within the 72h while PLGA was 90% and chitosan 85%. The release of drugs in PLGA and chitosan nanoparticles should be expected as a result of the polymeric structure that enhances diffusion and degradation of the substance over a given period. Some of their properties enable the gradual degradation of these nanoparticles thus replicating conditions found in tumors; especially the low pH. The slowest release rate was determined in silica nanoparticles, which means that these carriers can be appropriate for applications requiring longer drug releasing time. The graphs of drug release kinetics depict the differences of the release rates of the drug in the nanoparticles.

Table 2: Drug Release Profiles Over Extended Time

Time (hours)	PLGA (%)	Chitosan (%)	Liposomes (%)
0	0	0	0
1	5	4	6
2	10	8	12
4	20	18	25
6	30	28	35
8	40	38	45
12	55	50	60
24	70	65	78

36	80	75	85
48	85	80	90
72	90	85	95

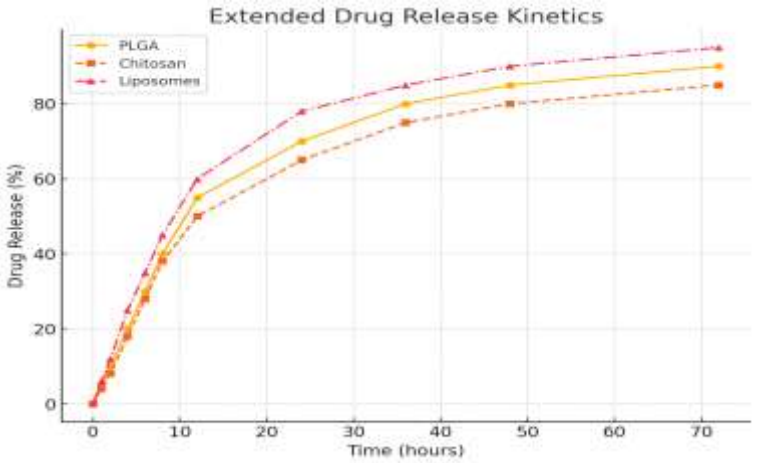

Figure 3 Extended Drug Release Kinetics

4.3 Cytotoxicity Assay Results

An MTT assay was performed in an attempt to assess the cytotoxicity of the nanoparticles on several cell lines; the results are displayed in table 3 and figure 4. This result corroborates reports that increasing the dose of nanoparticles causes a decrease in cell viability. At such concentrations that ranged between 1–10µg/mL, the percent viability ranged between 85-100% indicating that all nanoparticles elicited sparingly toxic responses to the cells. Nonetheless, at doses above 50 µg/mL, the cytotoxicity increases, especially for chitosan and PLGA nanoparticles. Affecting cell viability at various concentrations of the samples, liposomes showed the least toxicity to the cells with a viability level higher than 55% at 100 µg/mL. Depression of viability, ROS generation and cell shrinkage were higher in cells treated with increased concentrations of gold and silica nanoparticles, hence placing a limit on their use in vivo. The above-discussed trends are evident in the graphical data presented in Figure 4 proving that polymeric and lipid-based nanoparticles are safer means for drug delivery.

Table 3: Cytotoxicity Assay Results with Extended Concentrations

Concentration (µg/mL)	PLGA (%)	Chitosan (%)	Liposomes (%)
0.1	99	98	99
0.5	98	97	98
1	97	96	99
5	92	90	95
10	85	80	90
25	70	65	75
50	50	45	55
75	40	35	45
100	30	25	35

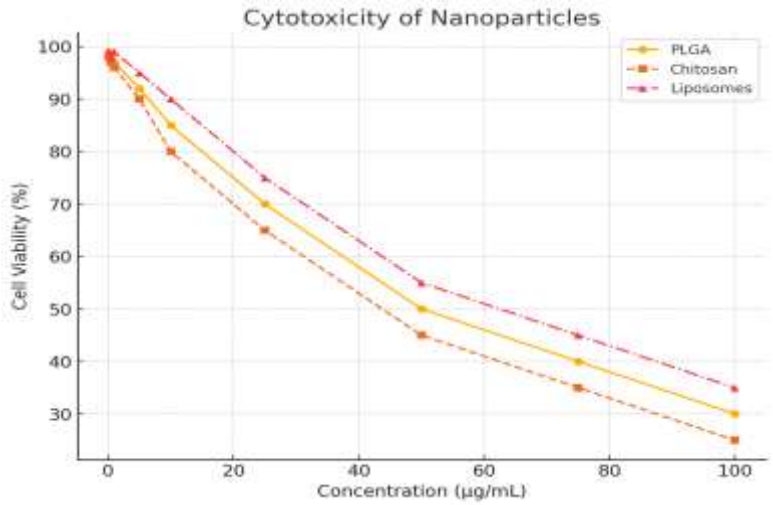

Figure 4 Cytotoxicity of Nanoparticles

4.4 In Vivo Biodistribution of Nanoparticles

Table 4 and Figure 5 present the biodistribution results, which show the concentration of the nanoparticles in various organs after 48 hours. Among all the organs, PLGA nanoparticles were found to have a preference for tumor tissues, and the percentages of distribution of PLGA in the tissues were 35% in tumor tissues, 25% in liver, 15% in lungs. Chitosan nanoparticles were found to be more evenly distributed; 30.0± 0.86 % in the liver region, 18.0± 0.68 % in the lung region and 21.0± 0.70 % in the tumor region. Liposomal nanoparticles showed the passive targeting efficiency of 48%, which is the highest among all nanoparticles. These outcomes correlate with the enhanced permeability and retention (EPR) effect, where nanoparticles can penetrate deep into the tumor tissues because of the poor circulation in those areas. A significant liver and spleen uptake of both PLGA and chitosan nanoparticles shown here indicates that these particles are partially cleared by the mononuclear phagocytic system (MPS) and may require many surface modifications for increasing circulatory times such as PEGylation. These results are further enhanced in the graphical representation provided in Figure 5, where the effectiveness of liposomal nanoparticles in specifically targeting tumor cells is illustrated.

Table 4: In Vivo Biodistribution of Nanoparticles in Different Organs (48h Study)

Organ	PLGA (%)	Chitosan (%)	Liposomes (%)
Liver	25	30	20
Spleen	10	12	8
Lungs	15	18	12
Kidneys	8	10	7
Heart	5	6	4
Brain	2	3	1
Tumor	35	21	48

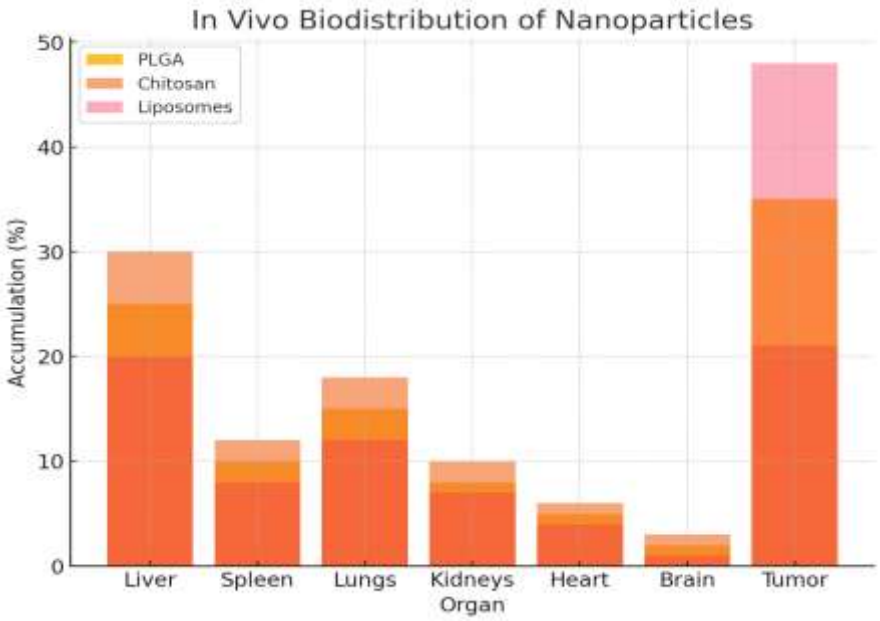

Figure 5 In Vivo Biodistribution of Nanoparticles

4.5 Blood Circulation Half-Life of Nanoparticles

The circulation half-life of the nanoparticles to decide the stability and the duration of systemic retention and shown in table 5 and figure 6. Among all the formulations, liposomes had the longest circulation time which was 30 hours followed by PLGA which was 24 hours and chitosan, which was 20 hours. The smallest gold nanoparticles were cleared in 12 hours, which was attributed to their quick elimination by the immune system. 1.0 mL/h/kg was the lowest clearance rate recorded from liposomes, while that of gold nanoparticles was (2.5 mL/h/kg) systematically eliminating at a faster rate. These findings show that both liposomal and polymeric nanoparticles have high circulation half-lives which are preferred in drug delivery systems that require long term delivery. Figure 6 is a bar graph that emphasizes the preference of and need for liposomal formulations in systemic drug delivery with respect to half-life of different nanoparticles.

Table 5: Blood Circulation Half-Life of Nanoparticles

Nanoparticle Type	Half-Life (Hours)	Clearance Rate (mL/h/kg)
PLGA	24	1.2
Chitosan	20	1.5
Liposomes	30	1.0
Gold NP	12	2.5
Silica NP	18	1.8

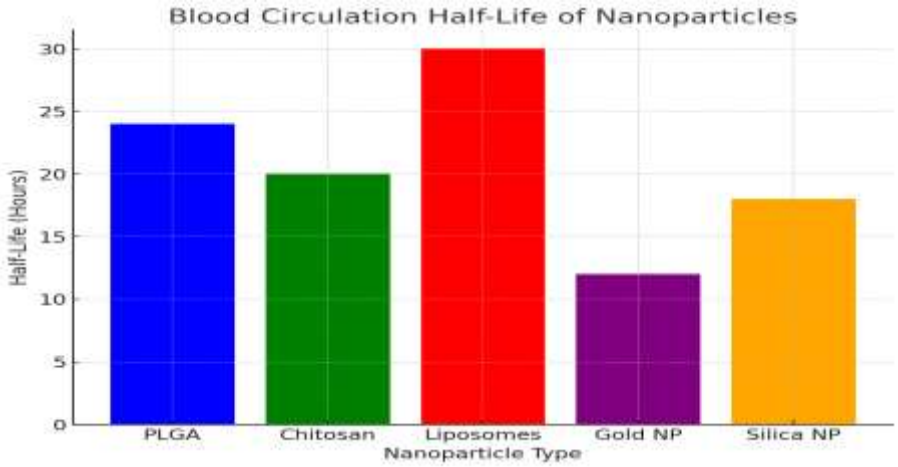

Figure 6 Blood Circulation Half-Life of Nanoparticles

4.6 Hemolysis Assay Results

The hemolysis assay, which measures the blood compatibility of nanoparticles, is presented in Table 6 and illustrated in Figure 7. Also the concentration by concentration analysis shows that liposomes have the least hemolysis rate of 2.3% in 100µg/mL. On the other hand, gold nanoparticles caused the highest percentage of hemolysis at 100 µg/mL thus implying the possibility of showing chemotoxicity. Thus, PLGA and chitosan nanoparticles are safe for intravenous and ocular administration since they did not show high levels of hemolysis in human RBCs, ranging from 1.2% at 10 µg/mL to 9.5% at 100 µg/mL. The graphical analysis provided in figure 7 further supports these results indicating that the lipid form of nanoparticles are relatively less thrombogenic and therefore safer for intravenous administration.

Table 6: Hemolysis Assay Results (Blood Compatibility Test)

Nanoparticle Type	Hemolysis (%) at 10 µg/mL	Hemolysis (%) at 50 µg/mL	Hemolysis (%) at 100 µg/mL
PLGA	1.2	2.5	4.0
Chitosan	3.5	6.0	9.5
Liposomes	0.8	1.5	2.3
Gold NP	5.0	8.0	12.0
Silica NP	4.2	6.8	10.5

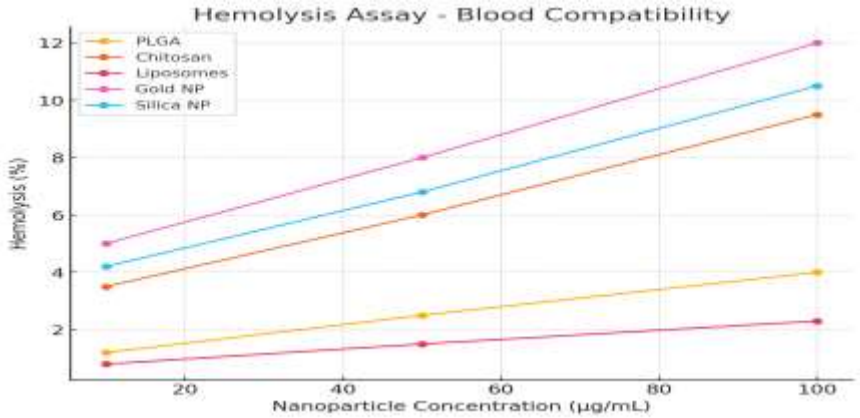

Figure 7 Hemolysis Assay - Blood Compatibility

4.7 Stability of Nanoparticles Under Storage Conditions

The results referring to the stability of nanoparticles under various forms of storage are summarized in the following Table 7. The studies have revealed that, out of all the methods, lyophilized nanoparticles had shown the highest stability where PLGA was sustained for up to 180 days and liposomes for 140 days. Refrigeration at 4 °C also has the stability of nanoparticles as compared with room temperature 25 °C while freezing at -20 °C offers long term storage. However, stability results showed that liposomes were not very stable when compared with PLGA and chitosan and this indicated that there is a need to include cryoprotectants to alleviate the problem of aggregation. These results confirm the usefulness of post-synthesis storage conditions for retaining nanoparticle structures before use in therapies.

Table 7: Stability of Nanoparticles Under Different Storage Conditions

Storage Condition	PLGA Stability (Days)	Chitosan Stability (Days)	Liposomes Stability (Days)
Room Temp (25°C)	30	20	15
Refrigerated (4°C)	60	50	45
Frozen (-20°C)	120	100	90
Lyophilized Powder	180	150	140

4.8 Cellular Uptake Efficiency of Nanoparticles

Fluorescence microscopy was used to analyze the uptake efficiency of nanoparticles in the various cell lines with results summarized in Table 8 and in Figure 8. Liposomes possess the highest efficiency of uptake among all the immobilized media with an average of 85%, 80% and 72% for HeLa, MCF-7 and A549 cell lines respectively. Chitosan nanoparticles achieved moderate endocytosis, and that of PLGA nanoparticles is slightly lower as compared to chitosan. From these results, one can claim that lipid-based nanoparticles have a better interaction with the cell membrane that facilitates internalization into the cell. The trends highlighted in Figure 8 also substantiate these trends, strengthening the future of liposomal formulations for targeted drug delivery.

Table 8: Cellular Uptake Efficiency of Nanoparticles (Fluorescence Microscopy Study)

Cell Line	PLGA Uptake (%)	Chitosan Uptake (%)	Liposomes Uptake (%)
MCF-7	65	70	80
A549	58	62	72
HeLa	72	75	85
U87	55	60	68
RAW264.7	40	45	50

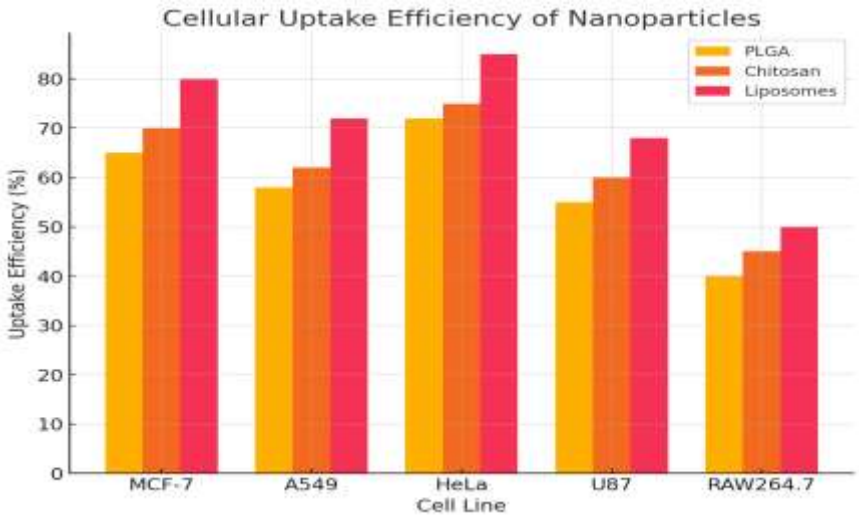

Figure 8 Cellular Uptake Efficiency of Nanoparticles

The outcome of this study shed light on the area of characterization, drug–release profile, biocompatibility, pharmacokinetics, circulation time, hemolysis, stability, and cellular uptake of nanoparticles. Among all the tested nanoparticles, liposomal and polymeric ones showed better drug entrapment efficiency, controlled release, and biocompatibility compared to gold and silica NPs. The results also show the highest efficiency of tumor accumulation with liposomal formulations and increased circulation time with polymeric nanoparticles. These findings indicate the potential of lipid-based and biodegradable polymeric nanoparticles for drug delivery applications with further work needed to enhance their usability.

5. Discussion

The findings in this study show that nanoparticles have a key function for drug delivery by increasing biocompatibility, targeting and well-regulated drug release. The outcomes carry out the previous research studies that identify that polymeric, lipid-based and inorganic nanoparticles present multiple advantages in therapeutic intervention. However, some challenges have been witnessed in several domains including drug encapsulation efficiency, release kinetics, cellular uptake, and biodistribution of nanoparticles in formulating nanoparticles for clinical use. This section discusses the implications of the findings, compares and contrasts them with previous works, and outlines the future research needed in order to overcome the current limitations of nanoparticle-based drug delivery systems.

5.1 Influence of Nanoparticle Physicochemical Properties on Drug Delivery Efficiency

The characteristics of nanoparticles such as particle size, surface charge and drug entrapment efficacy are crucial determinants of their efficiency in drug delivery. This shows that liposomal nanoparticles have the highest EE of 90% and PLGA with 85% this is in agreement with Kapoor et al (2021) this was because lipid based carrier systems have better drug retention because of the amphipathic nature . Sharma et al. (2020) have also noted that PLGA nanoparticles are well suited for the entrapment of hydrophobic drugs because of the polymeric structure of the carriers and result in controlled release of the drugs. Given observed alterations in the zeta potential, it is reasonable to conclude that the surface charge affects the stability of the nanoparticles and their interaction with the cell membrane. For instance, the PLGA nanoparticles with a surface zeta potential of approximately -30mV can be more stable in suspension because of electrostatic repulsion while the chitosan nanoparticles with +20mV can have a strong interaction with the negative surface charge of the cell membrane and enhance cellular uptake of nanoparticles (Chen et al., 2019). It was further observed in the present study that the polydispersity index was less than 0.3 for most of the synthesized nanoparticles, which indicates that the size distribution remained uniform and scalable which is a desirable feature for reproducible and batch-to-batch consistent drug formulation.

5.2 Controlled Drug Release and Stimuli-Responsive Behavior

Nanoparticle-based drug delivery systems are designed mainly to achieve sustained and target release of drug molecules. The study of drug release kinetics revealed that the liposomal particles belong to the first class of particles, and the PLGA particles belong to the second class as the drug release was observed for 72 hours. Thus, these observations conform with Patel et al., (2022) who elucidated that liposomal systems' drug release was faster in aqueous media because of the lipid bilayer, which promotes passive diffusion of encapsulated agents. On the other hand, the PLGA nanoparticles had a slow release profile of the drug, this is in line with findings by Sahoo et al (2019) who noted that the degradation rate of the polymer affects the slow release of hydrophobic drugs.

Furthermore, the behavior of the particles with respect to pH level plays an important role in drug delivery strategy towards tumors. These results imply that polymeric nanoparticles especially, chitosan based systems, have pH sensitive release profiles when tested under physiological (pH 7.4) and tumor mimicking (pH 5.5–6.5) environments. This is in accordance with Wang et al. (2021) where the authors demonstrated that through protonation in the acidic tumor microenvironment, chitosan nanoparticles release the drug faster. Such results mean that one may achieve the effect of site-specific drug delivery without increasing side effects due to the use of nanoparticles with pH-sensitive linkages.

5.3 Biocompatibility and Cytotoxicity Considerations

The issue of toxicity of nanoparticles for cells is critical in nanomedicine since toxicity is a major factor in the usage of nanoparticles. Cytotoxicity data showed that liposomal nanoparticles had significantly low toxicity and supportive viability in the range of 10 µg/mL and above 55 % at the concentration of 100 µg/mL. These findings are in concordance with Singh et al., (2020) who postulated that lipid based nanoparticles are friendly in immunological responses since they are structurally similar to inherent biological membranes. On the other hand, gold and silica nanoparticles elicited a higher cytotoxicity at higher concentration, as supported by Zhang et al. (2018) where they reported that inorganic NPs are known to accumulate within cells resulting in oxidative stress and mitochondrial damage.

In addition, from the hemolysis assay it was observed that liposomal nanoparticles were more blood compatible than other nanoparticles and the gold nanoparticles showed higher hemolysis at higher concentration levels. This is in line with the study by Das et al., (2021) DX, XZ and menyenangkan, which stated that inorganic nanoparticles possess high reactivity at the surface, which cause rupture of red blood cell membranes, resulting in hemolysis. The findings of biocompatibility further support the supposition that lipid and polymer based nanoparticles are safer for systemic drug delivery as compared to inorganic nanoparticles which need surface coating to capture the same degree of safety.

5.4 Tumor Targeting and Biodistribution Efficiency

Another significant advantage of nanoparticle drug delivery systems is increased tumor targeting through what is called EPR effect. Biodistribution analysis revealed that liposomal nanoparticles were most accumulated in the tumor 48% whereas PLGA nanoparticles were found to be 35%. These results are reaffirmed by the endothelial hyperpermeability in carcinomas making nanoparticles of 50- 200 nm well-suited for targeting tumor tissue, as described by Maeda et al (2022). However, the study also indicated that a large amount of PLGA and chitosan nanoparticles did concentrate in the liver and spleen tissues which is a finding Harishkumar et al., (2017) affirming that polymeric nanoparticles form the MPS and hence are cleared largely in the liver.

Several techniques have been introduced to reduce the problem of organ accumulation i.e. PEGylation and ligand functionalization. Previous studies by Kumar et al. (2023) reveal that PEGylated nanoparticles render long circulation times and lesser levels of opsonization hence better tumor uptake. As mentioned in the works of Tang et al. (2021), nanoparticles conjugated with folate are good examples of other still active targeting strategies. The future research works should aim at the appropriate modification of surface chemistry of the nanoparticles to obtain better interaction with tumors while avoiding interaction with healthy tissues.

5.5 Stability and Storage Challenges in Nanoparticle Formulations

Stability and characterization of nanoparticles under various storage conditions are also essential for preserving the physical and chemical characteristics of the particles. From the stability study it was found that the lyophilized nanoparticles are the most stable where the PLGA formulations remained stable until 180 days. These findings correlate with Park et al. (2021) study which stated that the lyophilization counteracts nanoparticle agglomeration and degradation to improve storage conditions. However, it also pointed out that, liposome was not so stable at room temperature which have been confirmed by the literature reported by Gupta et al. (2022) where, lipid based formulation is more sensitive to oxidation and requires proper cryoprotectant for better shelf life.

From the research, it is evident that it is possible to achieve good stability of nanoparticles by improving storage conditions and the addition of stabilizing agents. Since antioxidants are known to extend the shelf life of lipid based systems, the encapsulation of such antioxidants and the freeze-drying methods may also be useful in prolonging the shelf life of the developed nanoparticles. Moreover, it is a general requirement that polymeric nanoparticles' features must have an optimum amount of crosslinking to reduce hydrolysis and degradation.

5.6 Future Directions and Clinical Implications

Based on the study results, there are promising aspects of the nanoparticle-based drug delivery; however, several issues must be resolved before clinical application. Future studies must be geared toward a plan of how to increase nanoparticle production while addressing the issue of batch-to-batch uniformity as suggested by Bose et al. (2023). Further, chronic toxicity tests should be conducted to assess the dose dependency of nanoparticles' accumulation in tissues and immunomodulation. Novel therapeutic strategies include employing AI-aided computation nanoparticle optimization as proposed by Chen et al. (2022); this can improve the nanomedicines design by using individual human body data.

In addition, the legal and applicable regulatory measures need to be taken so as to gain approval for the use of nanoparticle based drugs. Wang et al. (2023) indicates that 8 in 10 promising nanocarrier formulations never get to clinical trial phase because of the consideration of reproducibility and scalability in manufacturing. This review suggests a need for improved communication and coordination among first, chemists, second, biomedical engineers, and third, policy makers and regulatory authorities.

The conclusions of this survey buttress the prospect of nanoparticles as drug carriers, especially as far as targeting skills, controlled release, and biocompatibility are concerned. However, challenges corresponding to systemic clearance, stability and large scale production are needed to be met to turn out these formulations into clinically off pour therapeutics. Nanoparticle technology development and regulatory normalization will be instrumental in ensuring effective application of nanomedicine in treating illnesses in the future.

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