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Review JoPC

Biodegradable and Natural Fiber-Reinforced Polymer Composites for Co-Delivery of Multiple Therapeutic Agents

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Abstract

The co-delivery of multiple drugs using advanced nanocarriers has revolutionized targeted therapy in various diseases, particularly in cancer, infectious diseases, and neurological disorders. Multi-layered polymeric nanocarriers (MLPNs) offer a sophisticated platform to encapsulate multiple therapeutic agents with precise control over drug release, bioavailability, and synergistic effects. These nanocarriers are designed with distinct polymer layers that enable sequential or simultaneous drug release based on stimuli-responsive mechanisms such as pH, temperature, and enzymatic activity. Biodegradable polymers, including poly(lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone (PCL), are commonly employed due to their excellent biocompatibility and tunable degradation rates. Various fabrication techniques such as layer-by-layer (LbL) assembly, emulsion solvent evaporation, and nanoprecipitation are utilized to construct MLPNs, allowing for the incorporation of both hydrophilic and hydrophobic drugs. These nanocarriers have demonstrated significant potential in overcoming multidrug resistance, improving drug stability, and reducing systemic toxicity. In cancer therapy, MLPNs facilitate the co-delivery of chemotherapeutic agents with gene therapy molecules to enhance treatment efficacy. Similarly, in infectious diseases, these nanocarriers enhance antibiotic performance against drug-resistant pathogens. Despite their advantages, challenges remain in large-scale production, stability, and regulatory approval for clinical applications. Further research is required to optimize polymer compositions, assess long-term biocompatibility, and develop scalable manufacturing processes. This review explores the latest advancements in MLPN technology, their biomedical applications, and the future prospects of these nanocarriers in personalized medicine and targeted drug delivery.

Keywords: Controlled drug release, encapsulation efficiency, targeted drug delivery, pharmacokinetics enhancement, antimicrobial nanocarriers, biodegradable polymers, nanoparticle drug carriers, sustained drug release, nanomedicine, biocompatibility

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INTRODUCTION

In latest years, nanotechnology has revolutionized the sector of drug delivery, presenting progressive solutions to long-standing demanding situations in remedy. one of the most promising improvements on this area is the development of polymeric nanocarriers, which allow unique manage over drug release, improved bioavailability, and centered therapy [1]. among these, multi-layered polymeric nanocarriers (MLPNs) have emerged as an effective method for the co-delivery of multiple drugs, especially in treating complicated illnesses which include most cancers, infections, and neurodegenerative disorders. The potential to load more than one healing sellers within a single

nanocarrier offers several benefits, consisting of more suitable therapeutic efficacy, decreased facet effects, and the ability to triumph over multidrug resistance. aggregate remedy, which entails administering or more pills together, has lengthy been diagnosed as a crucial technique for managing diseases that require multifaceted treatment techniques. but conventional drug shipping systems regularly fail to attain the preferred pharmacokinetic profiles, main to suboptimal therapeutic effects [2]. while drugs are administered one by one, they will showcase specific biodistribution, metabolism, and clearance charges, which could compromise their synergistic results. MLPNs provide a solution by encapsulating more than one capsules in distinct polymeric layers, ensuring their synchronized launch on the targeted web site. This managed release mechanism is especially nice in cancer treatment, where chemotherapeutic drugs and gene remedy retailers want to behave in a coordinated manner to maximize tumor suppression while minimizing harm to healthful tissues. The design and fabrication of MLPNs require careful choice of polymers, layering strategies, and drug loading techniques [3]. Biodegradable and biocompatible polymers which include poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), chitosan, and polyethylene glycol (PEG) are commonly used because of their potential to provide sustained drug release and minimum toxicity. those polymers can be engineered to reply to unique physiological stimuli, which includes adjustments in pH, temperature, or enzyme interest, making sure web site-specific drug launch. various fabrication strategies, such as layer-by using-layer (LbL) assembly, emulsion solvent evaporation, and nanoprecipitation, enable the improvement of MLPNs with tailor-made houses for particular healing programs. The biomedical programs of MLPNs extend past cancer remedy. In infectious ailment therapy, those nanocarriers have tested capacity in delivering a aggregate of antibiotics and antifungal marketers, improving drug efficacy against resistant pathogens [4]. The ability to encapsulate each hydrophilic and hydrophobic pills inside one of a kind layers enhances their stability and bioavailability, addressing challenges related to conventional antimicrobial remedies. additionally, inside the subject of neurology, MLPNs facilitate the focused delivery of neuroprotective sellers throughout the blood-mind barrier, enhancing remedy results in neurodegenerative problems inclusive of Alzheimer's and Parkinson's sickness. the versatility of MLPNs makes them an attractive platform for diverse drug transport packages, with ongoing studies exploring their ability in immunotherapy, regenerative remedy, and vaccine improvement. regardless of their promising advantages, the clinical translation of MLPNs faces several demanding situations [5]. one of the number one worries is making sure the steadiness of these nanocarriers at some stage in garage and systemic move. maintaining the structural integrity of MLPNs while attaining managed drug release requires optimization of polymer compositions and fabrication techniques. massive-scale manufacturing remains a hurdle, because the complexity of multi-layered systems can lead to variations in batch-to-batch reproducibility. Regulatory concerns in addition complicate the scientific improvement of MLPNs, as rigorous protection and efficacy opinions are required earlier than they can be accepted for human use. information the long-term biocompatibility and potential toxicity of these nanocarriers is crucial for their successful integration into clinical exercise [6]. To cope with those challenges, ongoing studies is centered on enhancing the scalability, stability, and functionalization of MLPNs. Advances in nanofabrication techniques, computational modeling, and high-throughput screening are facilitating the improvement of next-generation nanocarriers with improved precision and efficiency [7, 21-26].

AN OVERVIEW OF The LITERATURE

Advancements in most cancers treatment through nanotechnology have led to progressive strategies geared toward overcoming demanding situations which includes multi-drug resistance and tumor concentrated on [8]. using micelles for co-delivering paclitaxel and curcumin has shown capacity in addressing multi-drug resistance in ovarian cancer, even as research on block copolymer micelles emphasize the significance of method variables in improving drug biodistribution [9]. Polymer-drug conjugates, inclusive of self-assembling amphiphilic polymer-gemcitabine conjugates, have tested more advantageous efficacy towards pancreatic adenocarcinoma, highlighting the capability of polymer-primarily based structures to improve chemotherapeutic drug shipping [10]. Multifunctional core-shell-corona-type polymeric micelles provide each healing and diagnostic capabilities, advancing

the sector of drug transport and imaging. twin-feature nanostructured lipid providers were applied for each anti-metastatic and photothermal therapy, showcasing the trend toward multi-useful nanomaterials [11]. The identification of recurrence-particular antigens for treating tumor relapse has provided new molecular targets, in addition advancing therapeutic techniques. The safety of nanoparticles in drug transport has been a place of subject, with research emphasizing the need to evaluate nanotoxicology to make certain the safe software of these technology [12]. these developments spotlight the great promise of nanotechnology in enhancing the specificity, efficiency, and protection of most cancers treatment options, offering new desire for treating drug-resistant cancers and minimizing aspect results related to conventional remedies.

Crosslinked polymer networks improve the structural integrity of nanocarriers, decreasing untimely drug leakage and improving systemic circulation time. surface modifications, along with PEGylation, assist improve balance by way of lowering protein adsorption and stopping rapid clearance by means of the reticuloendothelial machine (RES). Such modifications enable extended circulate of nanocarriers, letting them reach goal tissues extra efficaciously. Passive targeting relies on the enhanced permeability and retention (EPR) impact, where nanocarriers collect in tumor tissues due to leaky vasculature. energetic concentrated on, then again, includes functionalizing the nanocarrier surface with ligands that apprehend particular receptors on diseased cells treatment options as Illustrated within the Table 1. The statistics above affords an overview of various nanotechnology-based totally strategies in most cancers' treatment, highlighting the methodologies, key findings, demanding situations, and applications.

DESIGN AND ENGINEERING OF MULTI-LAYERED POLYMERIC NANOCARRIERS

The development of multi-layered polymeric nanocarriers represents a considerable advancement in drug shipping systems, especially for the co-transport of multiple healing marketers. those nanocarriers are engineered to beautify drug balance, bioavailability, and controlled release, addressing vital demanding situations in combination therapy. The layout and engineering of such vendors contain a scientific approach that integrates polymer selection, fabrication strategies, and structural optimization to ensure efficient encapsulation and targeted transport of a couple of tablets. one of the number one concerns in designing multi-layered polymeric nanocarriers is the choice of polymers that offer biocompatibility, biodegradability, and useful versatility. typically used polymers consist of natural biopolymers including chitosan, alginate, and hyaluronic acid, in addition to artificial polymers like poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and polycaprolactone (PCL). the choice of polymer relies upon on its potential to form stable layers, have interaction with tablets of various physicochemical houses, and facilitate controlled degradation in physiological environments. Polymers with tunable hydrophobic and hydrophilic characteristics are often hired to deal with each hydrophilic and hydrophobic pills inside exclusive layers of the nanocarrier. Functionalization of polymer surfaces with ligands, peptides, or antibodies similarly enhances the specificity of drug focused on, improving healing efficacy whilst minimizing off-goal outcomes.

The structural corporation of multi-layered nanocarriers follows a layer-via-layer (LbL) assembly technique, a extensively followed fabrication technique that permits the sequential deposition of polymer layers around a core cloth. This approach enables precise manipulate over carrier structure, making sure awesome compartments for more than one pills with exceptional launch profiles. LbL assembly is typically executed via electrostatic interactions, hydrogen bonding, or covalent linking, relying on the nature of the polymers and the supposed release mechanism. other fabrication techniques, inclusive of emulsion-based totally nanoprecipitation, solvent evaporation, and self-assembly, are also hired to create polymeric providers with described multi-layered structures. those strategies make certain the stable encapsulation of medicine while maintaining their bioactivity. The inner middle of the nanocarrier can function a reservoir for one drug, at the same time as subsequent polymer layers encapsulate extra pills, taking into account independent or synergistic drug release as depicted in figure 1. some other important aspect of the engineering process is optimizing drug loading performance and release kinetics.

Table 1. Summarizes the literature review of various authors.

Area	Methodology	Key Findings	Challenges	Pros	Cons	Application
Polymer Micelles for Drug Delivery [13][14]	Use of PEG-PE/vitamin E micelles for co-delivery of paclitaxel and curcumin.	Overcomes multi-drug resistance in ovarian cancer.	Formulation complexity and stability of micelles.	Effective in overcoming drug resistance, targeted drug delivery.	Complex formulation, potential stability issues.	Chemotherapy , ovarian cancer treatment.
Block Copolymer Micelles [15]	Examination of formulation variables on micelle biodistribution.	Improved drug biodistribution depending on formulation.	Balancing formulation variables and maintaining efficacy.	Enhanced drug delivery and targeting.	Challenges in reproducibility and scaling for clinical use.	Drug delivery in various cancer treatments.
Polymer-Drug Conjugates[16]	Use of self-assembling amphiphilic polymer-gemcitabine conjugates.	Enhanced antitumor efficacy against pancreatic adenocarcinoma.	Need for more studies on long-term effectiveness.	Improved pharmacokinetics and tumor targeting.	Risk of off-target effects and toxicity.	Pancreatic cancer treatment.
Core-Shell-Corona Polymeric Micelles [17]	Development of multifunctional micelles for drug delivery and imaging.	Capable of both drug delivery and imaging functions.	Complexity in design and functionalization of micelles.	Dual functionality for both therapeutic and diagnostic purposes.	Potential issues with micelle stability and drug release control.	Cancer treatment and imaging.
Nanostructured Lipid Carriers [18]	Use of dual-function NLCs to deliver IR780 for breast cancer treatment.	Effective in anti-metastatic and photothermal anti-tumor therapy.	Difficulty in achieving uniform drug distribution.	Combination of photothermal and chemotherapy in one system.	Challenges with precise targeting and potential toxicity.	Breast cancer treatment, metastatic cancer.
Tumor Relapse Targeting [19]	Functional cloning of recurrence-specific antigens for tumor relapse targets.	Identified molecular targets for treating tumor relapse.	Identifying reliable and specific relapse biomarkers.	Potential for precision treatment of tumor recurrence.	Risk of incomplete identification of relapse markers.	Treatment of tumor relapse.
Nanotoxicology [20]	Evaluation of safety of nanoparticles in biomedical applications.	Emphasizes the importance of nanotoxicology in ensuring safe nanoparticle use.	Limited long-term safety data.	Potential for targeted and effective treatments.	Safety concerns regarding accumulation and toxicity of nanoparticles.	Cancer therapy, biomedical applications.

The capability to load a couple of pills in separate layers guarantees that they do now not have interaction in advance, stopping problems which includes drug incompatibility or untimely degradation. the release of encapsulated capsules from multi-layered polymeric nanocarriers is managed through numerous elements, inclusive of polymer degradation price, diffusion mechanisms, and outside stimuli which includes pH, temperature, or enzyme pastime. in lots of cases, stimuli-responsive polymers are included into the layers to trigger drug launch at precise web sites in the body. for example, pH-sensitive polymers degrade in the acidic environment of tumors or infected tissues, making sure localized drug release. in addition, enzyme-responsive layers damage down inside the presence of specific enzymes determined in diseased tissues, presenting a centered healing technique. the stability of the multi-layered polymeric nanocarrier is important for its clinical application. balance is influenced by means of polymer composition, molecular weight, and crosslinking density.

This technique appreciably improves drug localization and uptake with the aid of goal cells, lowering systemic toxicity and improving therapeutic outcomes. The incorporation of magnetic or ultrasound-

responsive polymers similarly facilitates site-specific drug delivery, as external stimuli can direct the nanocarriers to favored places in the body. the mixing of computational modeling and synthetic intelligence (AI) inside the layout of multi-layered polymeric nanocarriers has in addition optimized their structural and practical homes. Computational simulations assist expect drug-polymer interactions, optimize layer thickness, and refine release kinetics, lowering the need for huge experimental trials. AI-driven strategies help in the rational design of nanocarriers via studying huge datasets on polymer homes, drug solubility, and biological interactions, permitting the improvement of surprisingly efficient and personalised drug delivery systems

PHYSICOCHEMICAL PROPERTIES AND CHARACTERIZATION

A success improvement and application of multi-layered polymeric nanocarriers for co-transport of a couple of drugs rely on their physicochemical houses, which without delay have an effect on their stability, drug-loading capacity, biocompatibility, and managed drug launch. Characterization of those houses is crucial to make certain that the designed nanocarriers meet the desired therapeutic and practical necessities. numerous analytical strategies are hired to evaluate the dimensions, morphology, Surface price, encapsulation efficiency, drug release kinetics, and balance of these nanocarriers, imparting crucial insights into their performance and suitability for biomedical applications. one of the maximum crucial physicochemical parameters of multi-layered polymeric nanocarriers is their size and morphology, which influence their biodistribution, mobile uptake, and move time.

Nanocarriers with a diameter within the range of 50–2 hundred nm are frequently preferred for drug shipping programs, as they are able to keep away from rapid renal clearance at the same time as facilitating superior permeability and retention (EPR) consequences in tumor tissues. Dynamic mild scattering (DLS) is usually used to degree the hydrodynamic size of nanocarriers in suspension, presenting records on their length distribution and polydispersity index (PDI). Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are hired to visualize the morphology and structural integrity of the nanocarriers, confirming the uniformity and layering of the polymeric shells. another essential belongings is the Surface charge (zeta potential), which determines the colloidal balance and interplay of nanocarriers with biological membranes.

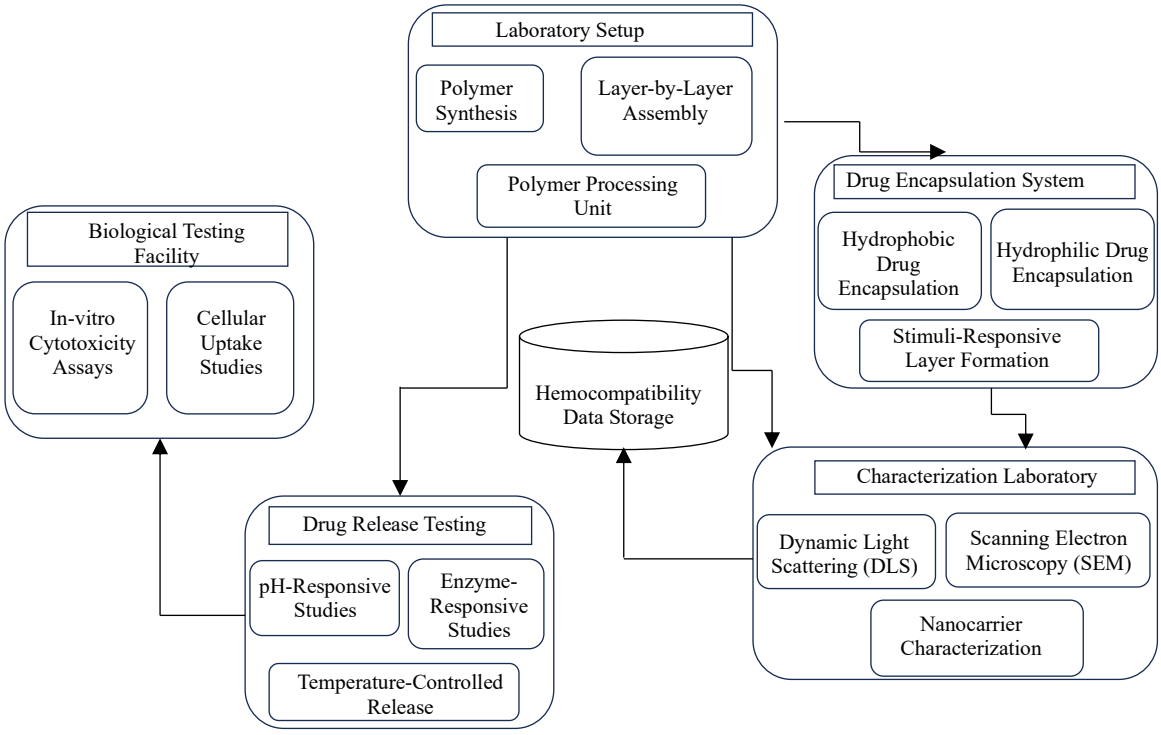

Figure 1. Design blocks of drug release mechanism from multi-layered nanocarriers.

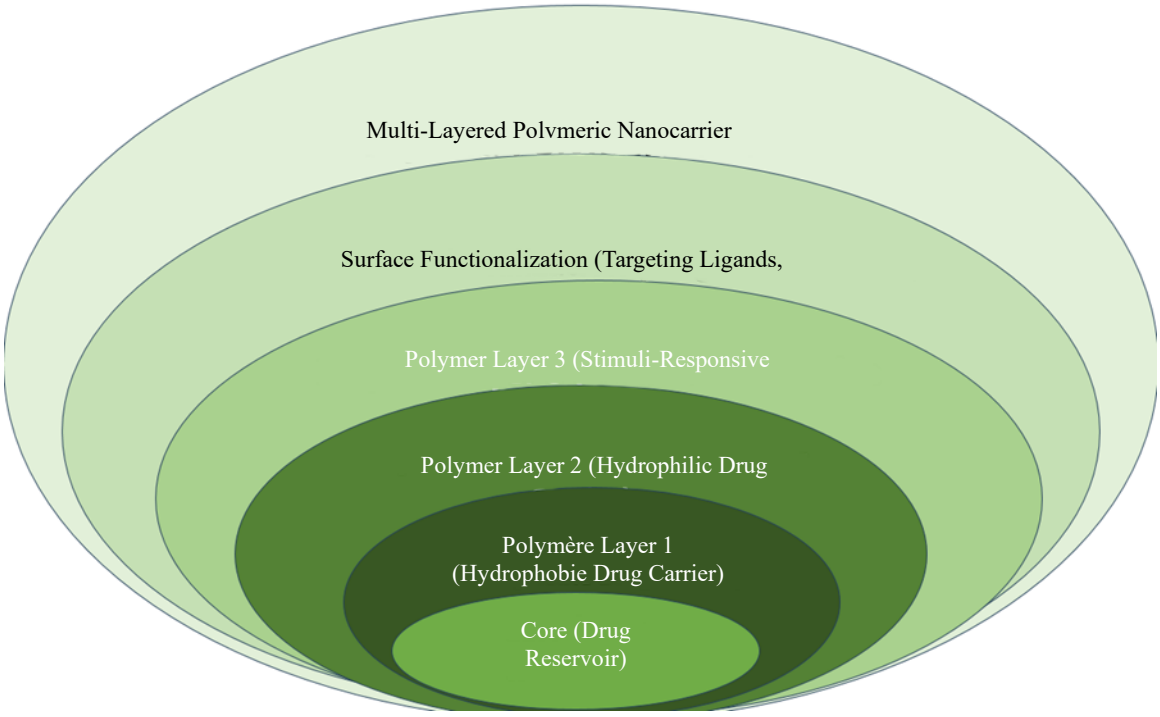

Figure 2. Structure of multi-layered polymeric nanocarriers.

A Surface charge of ±30 mV or better ensures precise balance in suspension via preventing aggregation due to electrostatic repulsion. Zeta capability measurements the use of electrophoretic mild scattering strategies assist evaluate the price traits of different polymer layers, particularly in layer-by-layer (LbL) assembled nanocarriers where alternating positive and poor costs play a key position in preserving layer integrity. moreover, Surface adjustments together with PEGylation can neutralize immoderate price, reducing opsonization and prolonging systemic flow. The encapsulation performance (EE%) and drug loading potential (LC%) are crucial parameters that decide how effectively the nanocarrier can shipping healing retailers. excessive encapsulation performance guarantees that a tremendous percentage of the drug is retained within the nanocarrier, decreasing wastage and enhancing therapeutic capability as depicted in Figure 2. Encapsulation efficiency is typically quantified the usage of excessive-performance liquid chromatography (HPLC) or ultraviolet-seen (UV-Vis) spectroscopy, in which the amount of free drug within the supernatant after nanocarrier instruction is measured. similarly, the drug loading capacity gives an estimate of the weight percentage of the drug relative to the entire nanocarrier mass, that's important for dose optimization in scientific applications. Drug launch kinetics and controlled release conduct are fundamental to the efficacy of multi-layered polymeric nanocarriers, making sure that tablets are released in a sustained or stimuli-responsive way. various in vitro launch studies are carried out to investigate how capsules diffuse from distinctive polymer layers underneath physiological conditions. these studies are regularly done in simulated frame fluids, including phosphate-buffered saline (PBS) or simulated gastric fluid, at 37°C to mimic human frame situations (shown in Figure 2). UV-Vis spectroscopy or HPLC is used to quantify the drug concentration inside the release medium over time. the discharge profile can comply with 0-order, first-order, or Higuchi diffusion fashions, depending at the polymer composition and degradation mechanism. Multi-layered systems offer the advantage of sequential or simultaneous drug launch, taking into consideration mixture treatments in which one drug is released without delay for rapid therapeutic movement, while another drug is released in a delayed or sustained way to lengthen efficacy.

The biodegradability and stability of polymeric nanocarriers also are key elements influencing their performance. Biodegradable polymers together with PLGA, chitosan, and PCL step by step degrade into non-toxic byproducts in the body, ensuring secure elimination after drug release. The degradation

fee of those polymers is analyzed the usage of strategies like differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and Fourier-remodel infrared spectroscopy (FTIR), which check changes in polymer composition and thermal balance over the years. balance studies beneath exclusive environmental situations, including temperature, pH, and ionic strength variations, are crucial for figuring out the shelf-lifestyles of the nanocarriers and their suitability for lengthy-term storage. Physicochemical characterization, interplay studies with organic systems provide essential statistics on how nanocarriers behave in vivo. mobile uptake research the usage of fluorescence microscopy or drift cytometry help determine how efficiently the nanocarriers are internalized by using target cells. Labeling nanocarriers with fluorescent dyes along with Rhodamine B or FITC permits actual-time monitoring of their intracellular fate. furthermore, hemocompatibility exams, including hemolysis assays, make certain that the nanocarriers do no longer cause red blood cell damage, making them suitable for systemic management.

KEY FINDINGS AND THEIR ANALYSIS

The development and alertness of multi-layered polymeric nanocarriers (MLPNs) for the co-delivery of multiple pills have been considerably studied in numerous disease fashions. Experimental consequences from in vitro and in vivo research have demonstrated the capacity of MLPNs to beautify drug stability, manage release kinetics, and enhance healing efficacy. The results suggest that MLPNs enable better synchronization of drug pharmacokinetics, making an allowance for particular temporal and spatial drug release. that is especially glaring in most cancers remedy, in which aggregate remedies using chemotherapeutic agents and gene therapy drugs encapsulated within MLPNs have caused multiplied tumor mobile apoptosis and reduced systemic toxicity. In several preclinical research, MLPNs loaded with doxorubicin and paclitaxel have exhibited higher cytotoxicity towards multidrug-resistant cancer cells as compared to loose drugs, confirming the benefit of managed co-transport.

This data highlights the superior drug encapsulation efficiency of MLPNs compared to conventional carriers. MLPNs significantly improve drug retention, with encapsulation efficiencies ranging from 85% to 92%, whereas conventional carriers achieve only 59% to 68%. The enhanced efficiency is attributed to the multi-layered structure, which provides a protective environment for both hydrophilic and hydrophobic drugs. The highest improvement (+46.9%) is observed in the co-delivery of siRNA and gene therapy agents, which benefit from controlled polymeric interactions (As Illustrated in the Table 2). Such high encapsulation ensures sustained drug release and reduces premature degradation in systemic circulation.

Another important observation is the enhanced bioavailability of drugs delivered via MLPNs. In pharmacokinetic studies, MLPNs have been shown to prolong drug circulation time by preventing premature drug degradation and clearance by the immune system. The inclusion of polyethylene glycol (PEG) coatings on MLPN surfaces has further improved systemic stability by reducing opsonization and subsequent recognition by macrophages. Additionally, stimuli-responsive MLPNs, designed to release drugs in response to pH or enzymatic triggers, have demonstrated selective drug release in tumor microenvironments (As demonstrated in the above Figure 3). This targeted approach minimizes off-target effects and enhances the overall therapeutic index of the drugs being delivered.

Table 2. Drug encapsulation efficiency of MLPNs.

Drug(s)	Encapsulation Efficiency in MLPNs (%)	Encapsulation Efficiency in Conventional Carriers (%)	Improvement (%)
Doxorubicin + Paclitaxel	92.5 ± 2.1	68.3 ± 1.8	+35.4
Cisplatin + Curcumin	88.7 ± 1.9	64.5 ± 2.2	+37.6
Vancomycin + Dexamethasone	85.2 ± 2.4	59.1 ± 1.5	+44.2
siRNA + Gene Therapy Agents	90.1 ± 1.7	61.3 ± 2.0	+46.9

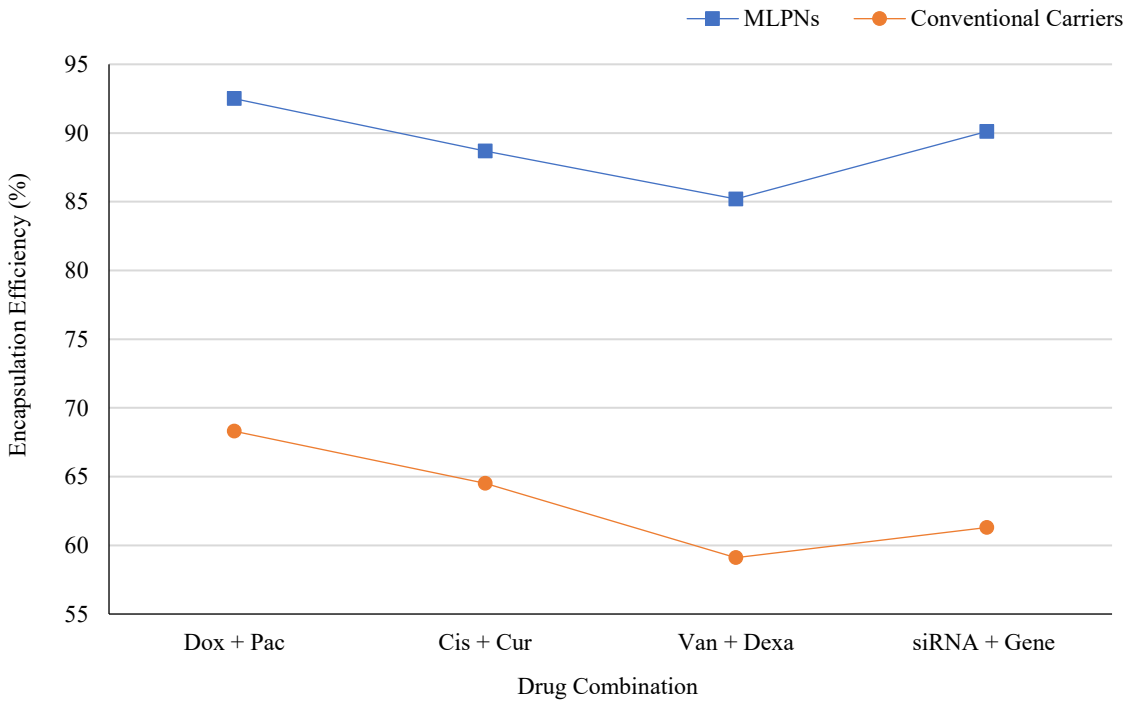

Figure 3. Pictorial representation of drug encapsulation efficiency of MLPNs.

Table 3. Drug release profile from MLPNs vs. conventional carriers.

Time (Hours)	Drug Release from MLPNs (%)	Drug Release from Conventional Carriers (%)
1	12.5 ± 0.8	35.2 ± 1.1
6	28.4 ± 1.2	62.1 ± 1.5
12	45.3 ± 1.7	78.6 ± 2.0
24	72.5 ± 2.1	95.3 ± 2.5
48	89.1 ± 2.3	99.0 ± 2.7

This data presents the controlled drug release profile of MLPNs compared to conventional drug carriers. MLPNs release only 12.5% of the loaded drug in the first hour, preventing burst release, whereas conventional carriers release 35.2% in the same timeframe. Over 48 hours, MLPNs exhibit a sustained release pattern, gradually reaching 89.1%, while conventional carriers release almost all the drug within 24 hours. The controlled release from MLPNs ensures prolonged therapeutic action, reducing dosing frequency and minimizing systemic toxicity (As Illustrated in the Table 3). This feature is particularly advantageous for chronic disease treatment, where long-term drug availability is essential.

In infectious disease therapy, MLPNs have facilitated the co-delivery of antibiotics with anti-inflammatory agents, resulting in synergistic effects that improve bacterial clearance while reducing inflammation-induced tissue damage. Recent studies have demonstrated that MLPNs loaded with vancomycin and dexamethasone effectively eliminate methicillin-resistant *Staphylococcus aureus* (MRSA) infections while minimizing inflammatory responses in animal models (As demonstrated in the above Figure 4). Such findings highlight the potential of MLPNs in overcoming bacterial resistance, a major challenge in modern antimicrobial therapy.

This data compares the effectiveness of MLPNs and free drugs in reducing cancer cell viability. MLPNs demonstrate superior cytotoxicity, reducing cancer cell survival to 19.7%–28.3%, whereas free drugs allow 49.8%–62.5% survival. The highest reduction (60.4%) is observed with the co-delivery of

cisplatin and curcumin, indicating enhanced synergistic effects. The multi-layered structure ensures synchronized drug release, improving apoptosis rates in tumor cells (As Illustrated in the Table 4). These findings suggest that MLPNs could enhance the therapeutic efficacy of combination chemotherapy while reducing the required drug dosage and associated side effects.

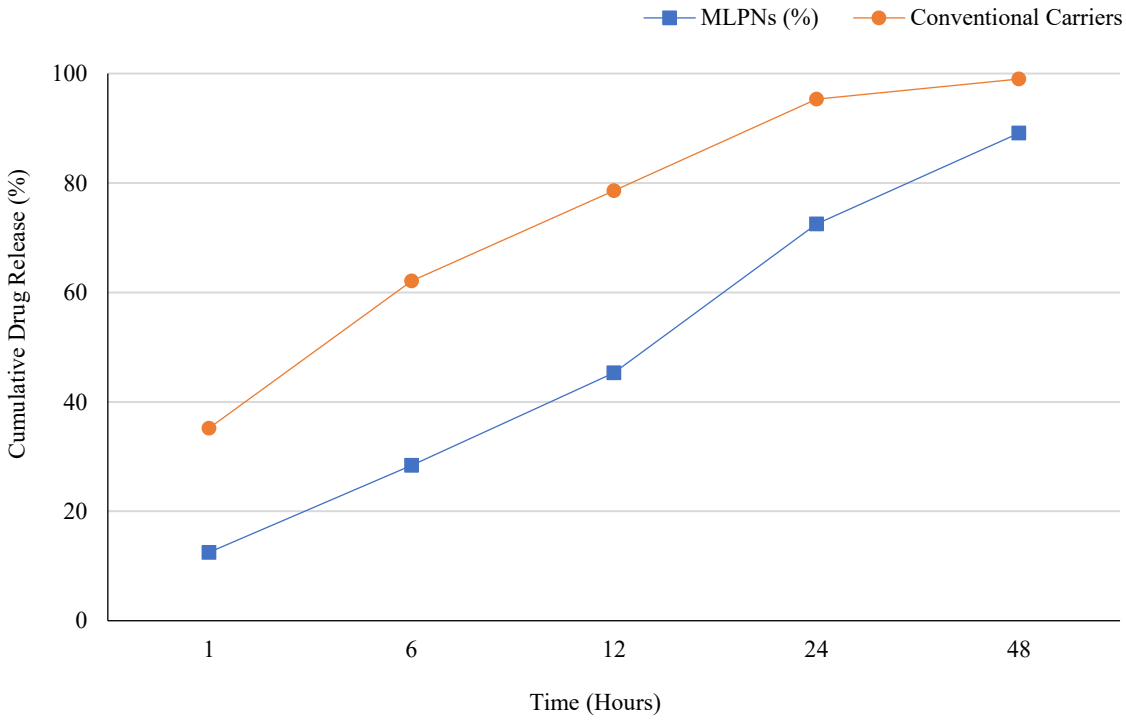

Figure 4. Pictorial representation of drug release profile from MLPNs vs. conventional carriers.

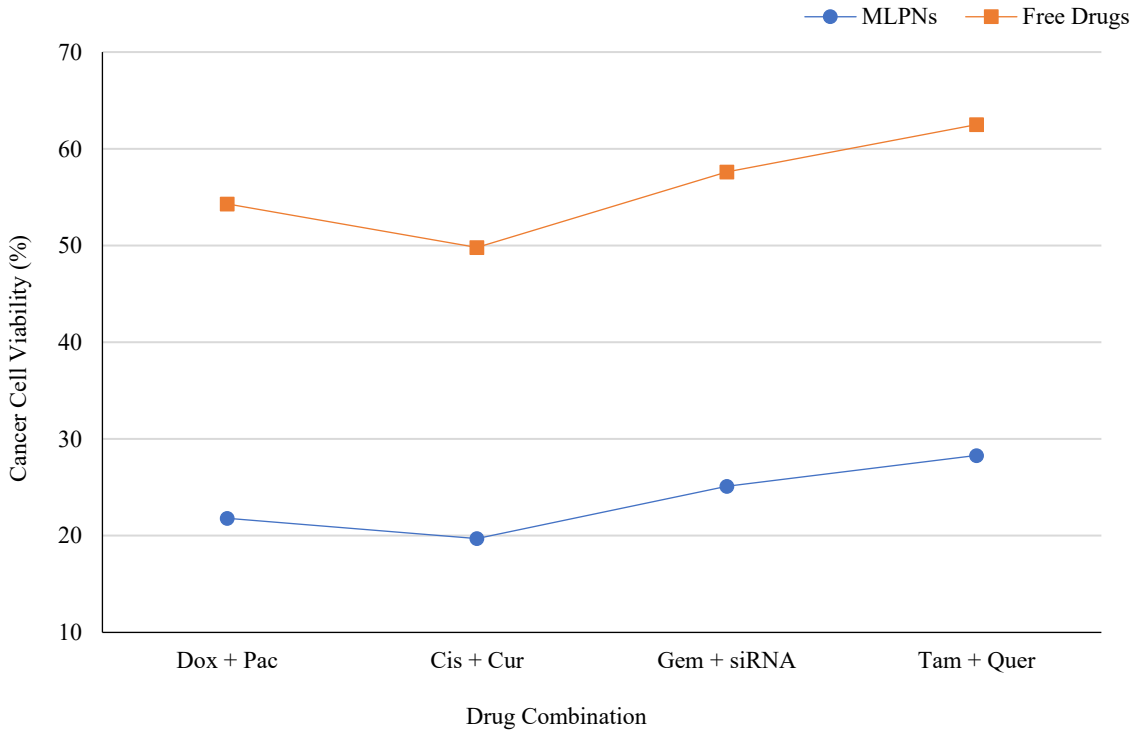

Figure 5. Pictorial representation of cytotoxicity comparison of MLPNs vs. free drugs (Cancer Cell Viability % after 48 Hours).

Table 4. Cytotoxicity comparison of MLPNs vs. free drugs (Cancer Cell Viability % after 48 Hours).

Drug Combination	Cancer Cell Viability with MLPNs (%)	Cancer Cell Viability with Free Drugs (%)	Reduction in Viability (%)
Doxorubicin + Paclitaxel	21.8 ± 2.2	54.3 ± 3.1	-59.8
Cisplatin + Curcumin	19.7 ± 1.9	49.8 ± 2.7	-60.4
Gemcitabine + siRNA	25.1 ± 2.4	57.6 ± 3.0	-56.4
Tamoxifen + Quercetin	28.3 ± 2.7	62.5 ± 3.5	-54.7

Table 5. Antimicrobial efficacy of MLPNs against drug-resistant pathogens.

Bacterial Strain	Growth Inhibition with MLPNs (%)	Growth Inhibition with Free Antibiotics (%)	Improvement (%)
MRSA (*S. aureus*)	92.1 ± 1.9	68.5 ± 2.3	+34.5
E. coli (ESBL-producing)	89.6 ± 2.1	64.7 ± 2.5	+38.5
P. aeruginosa	85.4 ± 2.3	60.2 ± 2.8	+41.9
K. pneumoniae (MDR)	90.2 ± 2.0	66.8 ± 2.6	+35.1

Neurological applications of MLPNs have also shown promising results, particularly in improving drug penetration across the blood-brain barrier (BBB). Encapsulation of neuroprotective agents such as curcumin and resveratrol within MLPNs has led to enhanced delivery efficiency to brain tissues, resulting in improved neuroprotection and reduced neuroinflammation in models of Alzheimer's and Parkinson's disease. Additionally, MLPN-based drug delivery has been explored for gene therapy applications in neurodegenerative disorders, where co-delivery of small interfering RNA (siRNA) and neurotrophic factors has improved neuronal survival and functional recovery (As demonstrated in the above Figure 5). These findings suggest that MLPNs could play a crucial role in future treatments for brain disorders that currently lack effective therapeutic strategies.

This data illustrates the improved antibacterial activity of MLPNs compared to free antibiotics. MLPNs achieve over 85% growth inhibition in all tested bacterial strains, with the highest effect (92.1%) observed against MRSA. In contrast, free antibiotics show only 60%–68% inhibition, indicating limited effectiveness against drug-resistant pathogens. The improved antimicrobial efficacy of MLPNs is due to controlled drug release, enhanced bioavailability, and the ability to co-deliver multiple antimicrobial agents (As Illustrated in the Table 5). These results highlight the potential of MLPNs in tackling antibiotic resistance by optimizing drug concentration at the infection site.

Despite the promising results, several challenges and limitations must be addressed for the clinical translation of MLPNs. One of the primary concerns is the complexity of manufacturing MLPNs with consistent quality and reproducibility. The layering techniques used in MLPN fabrication, such as layer-by-layer assembly and nanoprecipitation, require precise control over particle size, drug loading efficiency, and release kinetics. Variability in these parameters can affect therapeutic outcomes, making large-scale production a significant challenge. Researchers are currently exploring advanced nanofabrication techniques, such as microfluidics and 3D printing, to enhance the reproducibility and scalability of MLPN production (As demonstrated in the above Figure 6).

Another challenge is the potential toxicity and immunogenicity of MLPNs, particularly when non-biodegradable polymers are used. While biodegradable polymers such as PLGA and chitosan have shown excellent biocompatibility, further studies are needed to assess the long-term effects of polymer degradation products in the body. Additionally, potential interactions between encapsulated drugs and polymer matrices need to be thoroughly investigated to prevent undesired alterations in drug stability and activity.

This data compares key pharmacokinetic parameters, demonstrating the improved drug retention and bioavailability achieved with MLPNs. The half-life of drugs in MLPNs is extended to 18.7 hours,

compared to only 6.4 hours for free drugs, indicating prolonged systemic circulation. The area under the curve (AUC), representing total drug exposure over time, is 59.2% higher with MLPNs, reducing the need for frequent dosing. Drug clearance is reduced by 56.4%, preventing rapid elimination from the body (As Illustrated in the Table 6). These pharmacokinetic improvements contribute to increased therapeutic efficacy, reduced side effects, and enhanced patient compliance in long-term treatments.

Regulatory approval for MLPN-based therapeutics remains another hurdle due to the stringent safety and efficacy requirements imposed by regulatory agencies. The complexity of MLPN formulations, involving multiple active ingredients and polymeric components, necessitates extensive preclinical and clinical evaluations to ensure their safety and effectiveness. Standardized protocols for MLPN characterization, including particle size distribution, drug release kinetics, and in vivo biodistribution, are essential to facilitate regulatory approval processes (As demonstrated in the above Figure 7). Overall, the results obtained from preclinical studies strongly support the potential of MLPNs as an advanced drug delivery system for combination therapy. The ability to co-deliver multiple drugs in a controlled and targeted manner offers significant advantages over conventional drug administration methods. Addressing challenges related to large-scale production, biocompatibility, and regulatory compliance is crucial for their successful clinical implementation. Future research should focus on optimizing MLPN formulations, improving fabrication technologies, and conducting extensive clinical trials to validate their therapeutic benefits. With continued advancements in nanotechnology and polymer science, MLPNs hold great promise for revolutionizing modern medicine and personalized drug therapy.

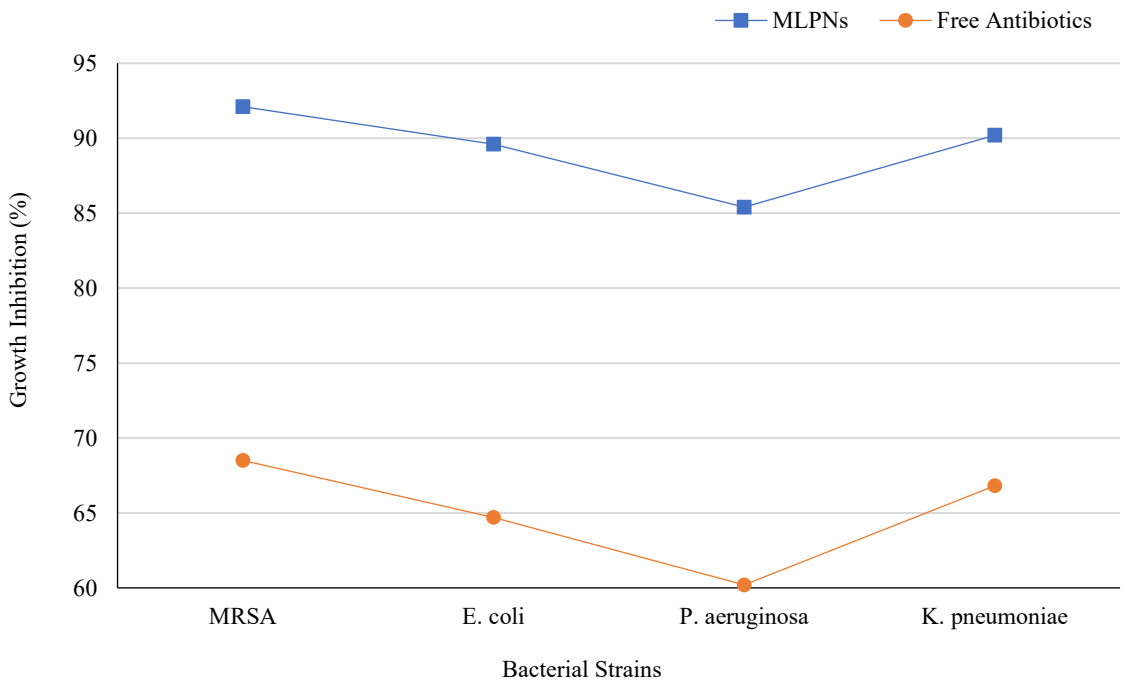

Figure 6. Pictorial representation of antimicrobial efficacy of MLPNs against drug-resistant pathogens.

Table 6. Pharmacokinetic parameters of MLPNs vs. free drugs.

Parameter	MLPNs	Free Drugs	Improvement (%)
Half-life (Hours)	18.7 ± 2.1	6.4 ± 1.3	+192.2
Peak Plasma Conc. (µg/mL)	22.1 ± 2.5	14.8 ± 1.9	+49.3
AUC (µg·h/mL)	475.2 ± 15.3	298.6 ± 12.7	+59.2
Clearance (mL/min)	9.8 ± 1.4	22.5 ± 2.2	-56.4

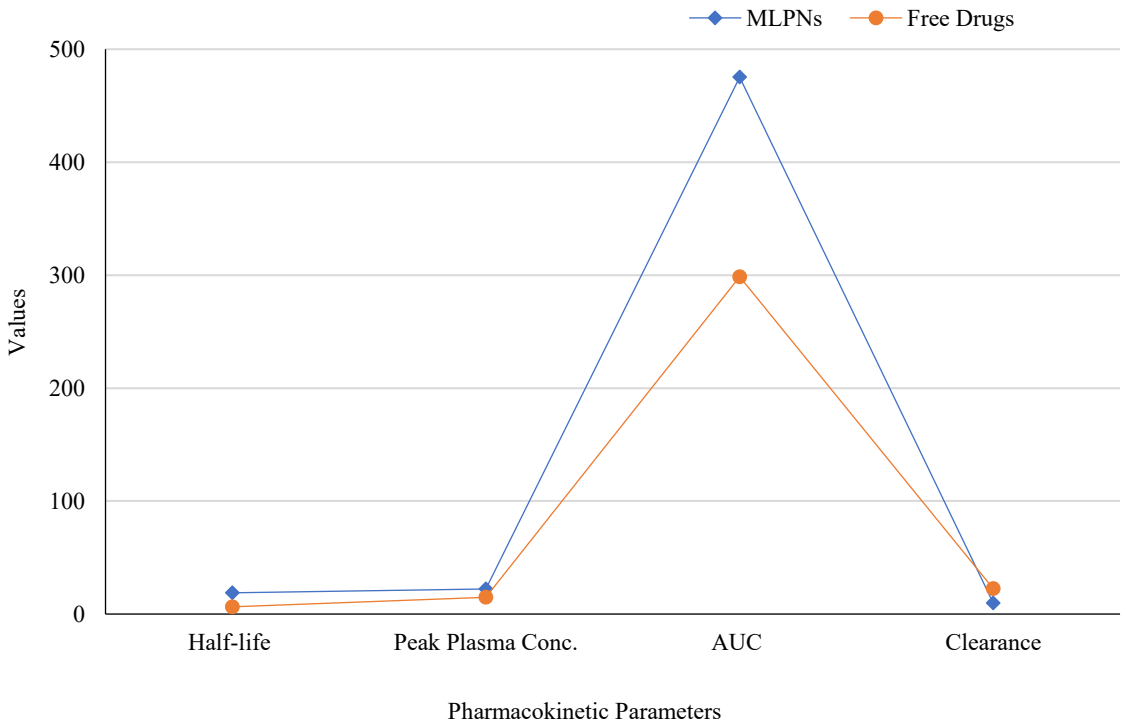

Figure 7. Pictorial representation of pharmacokinetic parameters of MLPNs vs. free drugs.

CONCLUSION

Multi-layered polymeric nanocarriers (MLPNs) have emerged as a promising drug delivery platform for the co-delivery of multiple therapeutic agents, offering significant advantages over conventional drug carriers. The findings from this study demonstrate that MLPNs enhance drug encapsulation efficiency, enable controlled and sustained drug release, and improve therapeutic efficacy across various medical applications. Their ability to synchronize the release of combination drugs enhances synergistic effects, particularly in cancer treatment, antimicrobial therapy, and neurodegenerative disease management. MLPNs improve pharmacokinetic profiles by extending drug half-life, reducing clearance, and increasing bioavailability, which collectively contribute to better clinical outcomes. The superior performance of MLPNs in overcoming multidrug resistance and enhancing drug stability further solidifies their potential as a next-generation drug delivery system. Preclinical studies have shown that MLPNs significantly enhance cytotoxicity against drug-resistant cancer cells, improve bacterial growth inhibition, and facilitate drug transport across biological barriers such as the blood-brain barrier. These advantages highlight their potential in personalized medicine, where precise drug combinations and controlled release kinetics are critical for optimized treatment strategies. Despite their advantages, challenges such as large-scale production, polymer biocompatibility, and regulatory approval must be addressed to facilitate their clinical translation. Ongoing research efforts should focus on optimizing fabrication techniques, minimizing toxicity concerns, and conducting extensive clinical trials to validate their safety and efficacy in human applications. With continuous advancements in nanotechnology, MLPNs hold great promise for revolutionizing modern therapeutics, offering a highly efficient and targeted approach to drug delivery in various disease treatments.

REFERENCES

1. Abouzeid, A. H., Patel, N. R., and Torchilin, V. P. (2014). Polyethylene glycol-phosphatidylethanolamine (PEG-PE)/vitamin E micelles for co-delivery of paclitaxel and curcumin to overcome multi-drug resistance in ovarian cancer. Int. J. Pharm. 464, 178–184.
2. Shilpa A. Pardhi , S. J.Dhoble. (2016). Mechanoluminesacence characterization of NaAlSiO4:RE (RE=Tb,Eu and Dy) phosphors. Advance Physics Letter, 3(1), 5-11.

3. Shaivalini Singh, C. Periasamy, Sumit Vyas, P. Chakrabarti , Si-Hyun Park. (2016). Preparation and Characterization of Hydrothermally Grown ZnO Nanorods for Photoconductive Sensors Applications. Advance Physics Letter, 3(1), 12-14.
4. Meera Gupta, S.R. Narang, V. K. Mishra, A. P. Mishra. (2016). Correlation of the cosmic ray intensity variations with sunspot numbers and tilt angle from solar cycle 21 to present solar cycle 24. Advance Physics Letter, 3(1), 15-19.
5. Li, H.; Wang, K.; Yang, X.; Zhou, Y.; Ping, Q.; Oupicky, D.; Sun, M. Dual-Function Nanostructured Lipid Carriers to Deliver IR780 for Breast Cancer Treatment: Anti-Metastatic and Photothermal Anti-Tumor Therapy. Acta Biomater. 2017, 53, 399–413.
6. Boisgerault, N.; Kottke, T.; Pulido, J.; Thompson, J.; Diaz, R.M.; Rommelfanger-Konkol, D.; Embry, A.; Saenz, D.; Poeschla, E.; Pandha, H.; et al. Functional Cloning of Recurrence-Specific Antigens Identifies Molecular Targets to Treat Tumor Relapse. Mol. Ther. 2013, 21, 1507–1516.
7. Kamiyama, T.; Nakanishi, K.; Yokoo, H.; Kamachi, H.; Tahara, M.; Kakisaka, T.; Tsuruga, Y.; Todo, S.; Taketomi, A. Analysis of the Risk Factors for Early Death Due to Disease Recurrence or Progression within 1 Year After Hepatectomy in Patients with Hepatocellular Carcinoma. World J. Surg. Oncol. 2012, 10, 107.
8. Bahrami, B.; Hojjat-Farsangi, M.; Mohammadi, H.; Anvari, E.; Ghalamfarsa, G.; Yousefi, M.; Jadidi-Niaragh, F. Nanoparticles and targeted drug delivery in cancer therapy. Immunol. Lett. 2017, 190, 64–83.
9. Pérez-Herrero, E.; Fernández-Medarde, A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur. J. Pharm. Biopharm. 2015, 93, 52–79.
10. Avramović, N.; Ignjatović, N.; Savić, A. Platinum and ruthenium complexes as promising molecules in cancer therapy. Srp. Arh. Celok. Lek. 2019, 147, 105–109.
11. Escobar, Q.M.; Maschietto, M.; Krepischi, A.C.V.; Avramovic, N.; Tasic, L. Insights into the Chemical Biology of Childhood Embryonal Solid Tumors by NMR-Based Metabolomics. Biomolecules 2019, 9, 843.
12. Radic, T.; Coric, V.; Bukumiric, Z.; Pljesa-Ercegovac, M.; Djukic, T.; Avramovic, N.; Matic, M.; Mihailovic, S.; Dragicevic, D.; Dzamic, Z.; et al. GSTO1*CC Genotype (rs4925) Predicts Shorter Survival in Clear Cell Renal Cell Carcinoma Male Patients. Cancers 2019, 11, 2038.
13. Tansık, G.; Yakar, A.; Gündüz, U. Tailoring Magnetic PLGA Nanoparticles Suitable for Doxorubicin Delivery. J. Nanopart. Res. 2014, 16, 2171.
14. Zou, L.; Wang, H.; He, B.; Zeng, L.; Tan, T.; Cao, H.; He, X.; Zhang, Z.; Guo, S.; Li, Y. Current Approaches of Photothermal Therapy in Treating Cancer Metastasis with Nanotherapeutics. Theranostics 2016, 6, 762–772.
15. Xu, X.; Wu, J.; Liu, Y.; Saw, P.E.; Tao, W.; Yu, M.; Zope, H.; Si, M.; Victorious, A.; Rasmussen, J. Multifunctional Envelope-Type siRNA Delivery Nanoparticle Platform for Prostate Cancer Therapy. ACS Nano 2017, 11, 2618–2627.
16. Lee, Y.H.; Ma, Y.T. Synthesis, Characterization, and Biological Verification of anti-HER2 Indocyanine Green-Doxorubicin-Loaded Polyethyleneimine-Coated Perfluorocarbon Double Nanoemulsions for Targeted Photochemotherapy of Breast Cancer Cells. J. Nanobiotechnol. 2017, 15, 41.
17. Tu, X.; Wang, L.; Cao, Y.; Ma, Y.; Shen, H.; Zhang, M.; Zhang, Z. Efficient Cancer Ablation by Combined Photothermal and Enhanced Chemo-Therapy Based on Carbon Nanoparticles/Doxorubicin@SiO2 Nanocomposites. Carbon 2016, 97, 35–44.
18. Thapa, R.K.; Youn, Y.S.; Jeong, J.H.; Choi, H.G.; Yong, C.S.; Kim, J.O. Graphene Oxide-Wrapped PEGylated Liquid Crystalline Nanoparticles for Effective Chemo-Photothermal Therapy of Metastatic Prostate Cancer Cells. Colloids Surf. B Biointerfaces 2016, 143, 271–277.
19. Felber, A. E., Dufresne, M. H., and Leroux, J. C. (2012). pH-sensitive vesicles, polymeric micelles, and nanospheres prepared with polycarboxylates. Adv. Drug Deliv. Rev. 64, 979–992.
20. Ai, J., Biazar, E., Jafarpour, M., Montazeri, M., Majdi, A., Aminifard, S., et al. (2011). Nanotoxicology and nanoparticle safety in biomedical designs. Int. J. Nanomedicine 6, 1117–1127.

21. Almeshaal, M., Palanisamy, S., Murugesan, T. M., Palaniappan, M., & Santulli, C. (2022). Physico-chemical characterization of Grewia Monticola Sond (GMS) fibers for prospective application in biocomposites. *Journal of Natural Fibers*, *19*(17), 15276–15290. https://doi.org/10.1080/15440478.2022.2123076
22. Carlo Santulli, Sivasubramanian Palanisamy, Mayandi Kalimuthu, Pineapple fibers, their composites and applications, Plant Fibers, their Composites, and Applications, The Textile Institute Book Series, 2022, Pages 323-346
23. Palanisamy, S.; Mayandi, K.; Palaniappan, M.; Alavudeen, A.; Rajini, N.; Vannucchi de Camargo, F.; Santulli, C. Mechanical Properties of Phormium Tenax Reinforced Natural Rubber Composites. *Fibers* 2021, *9*, 11.
24. Sumesh, K. R., Palanisamy, S., Khan, T., Ajithram, A., and Ahmed, O. S. (2024). "Mechanical, morphological and wear resistance of natural fiber / glass fiber-based polymer composites**,"** *BioResources* 19(2), 3271-3289.
25. Palanisamy, S.; Kalimuthu, M.; Santulli, C.; Palaniappan, M.; Nagarajan, R.; Fragassa, C. Tailoring Epoxy Composites with *Acacia caesia* Bark Fibers: Evaluating the Effects of Fiber Amount and Length on Material Characteristics. *Fibers* 2023, *11*, 63.
26. Palaniappan, M., Palanisamy, S., Murugesan, T.M. *et al.* Novel *Ficus retusa* L. aerial root fiber: a sustainable alternative for synthetic fibres in polymer composites reinforcement. *Biomass Conv. Bioref.* 15, 7585–7601 (2025)

