Keywords
Nanotechnology; Drug delivery; Nanotoxicity; Antimicrobial nanoparticles; liposomes

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Received:05-06-2026
Revised:10-07-2026
Accepted:15-07-2026
Doi:10.1922/ejprd.v34i7s.1592

Nanotechnology-Based Drug Delivery Systems: Biochemical Interactions, Microbial Responses, and Clinical Applications

Abstract
Drug delivery systems based on nanotechnology have the potential to develop therapeutic targeting, controlled release, antimicrobial activity, and biological transport. This study combined 1,000 harmonized records of 394 observations related to metal-oxide nanotoxicity, 318 observations related to antimicrobial activity of silver nanoparticles, and 288 PLGA or liposome formulations. Descriptive statistics, non-parametric test, and correlation analysis were used for the analysis of physicochemical and microbial and formulation variables. In total, 24.9% of the metal-oxide nanoparticles were found to be toxic, with CuO and ZnO the most toxic. Larger particle size, higher zeta potential, lower surface area, longer exposure and higher dose were found to correlate with toxicity. No significant differences were found between the MICs of Gram-positive and Gram-negative bacteria, but there was a weak positive correlation between the particle size and the MIC. The preparation method was a key factor in the antimicrobial activity, as the physical and green-synthesis methods generally had lower MIC values compared to the chemical reduction method. The performance of liposomes was better than that of the other formulations, as evaluated by their smaller size, low polydispersity, high encapsulation efficiency, and increased blood–brain-barrier transport. PLGA formulations exhibited higher degradation potential, sustained-release properties and stability. These results show that there are no universal characteristics of nanoparticles or carriers that will yield optimal results. Integrated assessment of safety, antimicrobial efficacy, delivery efficiency, barrier transport, biocompatibility and off-target effects is thus needed for development of nanomedicine. The formulation findings should be considered preliminary and exploratory.

1. INTRODUCTION

Drug delivery systems based on nanotechnology have the potential to develop therapeutic targeting, controlled release, antimicrobial activity, and biological transport. This study combined 1,000 harmonized records of 394 observations related to metal-oxide nanotoxicity, 318 observations related to antimicrobial activity of silver nanoparticles, and 288 PLGA or liposome formulations. Descriptive statistics, non-parametric test, and correlation analysis were used for the analysis of physicochemical and microbial and formulation variables. In total, 24.9% of the metal-oxide nanoparticles were found to be toxic, with CuO and ZnO the most toxic. Larger particle size, higher zeta potential, lower surface area, longer exposure and higher dose were found to correlate with toxicity. No significant differences were found between the MICs of Gram-positive and Gram-negative bacteria, but there was a weak positive correlation between the particle size and the MIC. The preparation method was a key factor in the antimicrobial activity, as the physical and green-synthesis methods generally had lower MIC values compared to the chemical reduction method. The performance of liposomes was better than that of the other formulations, as evaluated by their smaller size, low polydispersity, high encapsulation efficiency, and increased blood–brain-barrier transport. PLGA formulations exhibited higher degradation potential, sustained-release properties and stability. These results show that there are no universal characteristics of nanoparticles or carriers that will yield optimal results. Integrated assessment of safety, antimicrobial efficacy, delivery efficiency, barrier transport, biocompatibility and off-target effects is thus needed for development of nanomedicine. The formulation findings should be considered preliminary and exploratory.Nanotechnology-based drug delivery systems have emerged as versatile platforms in order to enhance the solubility, stability, circulation, targeting and controlled release of therapeutic agents. Nanocarriers can be designed to deliver small molecules, proteins, nucleic acids and combination therapies to the site of disease, in addition to safeguarding them from early degradation, unlike conventional dosage forms. Physicochemical properties, such as particle size, shape, surface charge, composition, and surface functionalization, play an important role in the biological distribution, cellular uptake, therapeutic activity, and toxicity of these materials. As a result, rational design of nanoparticles is complex and necessities to take into account both material properties and the biological environment that will be encountered following administration (1).

The most widely studied nanocarriers include lipid nanoparticles and polymeric systems. Lipid-based carriers offer excellent biocompatibility, tunable surface chemistry, and the ability to encapsulate hydrophilic, hydrophobic and nucleic-acid payloads (2). The biodegradability, formulation flexibility, and ability of the PLGA nanoparticles to release the drug gradually are significant attributes to such materials and make them particularly valuable (3). Through variations in carrier architecture, it is possible to create significant differences in terms of payload encapsulation and cellular transport (lipid vs. polymeric), as well as in terms of structural stability and release duration (lipid vs. polymeric). The distinct differences in these are important to consider when choosing a delivery platform for a particular therapeutic use. Nanoparticles after administration interact with proteins, lipids, membranes, immune components and extracellular matrices. These interactions can affect their surface identity, their pharmacokinetics, and also their biological activity. Thus, the biodistribution and clearance depend not only on the formulation used, but also on the interactions between the original formulation and physiological systems (4).

Biomolecular corona formation can also impact cellular recognition, uptake, toxicity and drug-release behaviour (5). In the field of cancer therapy, nanoparticles need to further pass through the vascular barriers, enter into tumour tissue and reach the target cells with an adequate concentration (6). These processes are particularly difficult in brain-directed delivery, in which most therapeutic molecules are unable to pass through the blood–brain barrier. Nanotechnology has also the potential to solve the problems of microbial infections and antimicrobial resistance. Nanomaterials can be used for drug delivery or have direct antimicrobial properties by causing oxidative stress and damaging membranes, as well as by releasing metal-ions and disrupting cellular processes (7). One of the most notable characteristics of the silver nanoparticles is that they could be effective against both Gram-positive and Gram-negative bacteria (8). But factors such as particle size, their shape, the way they are synthesized, how they are coated, their concentration, exposure time and the microbial strain of the microorganism are all factors that affect their antimicrobial performance.

Biofilms pose another hurdle because they have the ability to create a barrier that hinders the penetration of drugs and also shields microorganisms from typical treatments (9). Polymeric nanocarriers have the potential to increase antimicrobial retention, slow the release and provide penetration in biofilm associated environments (10). There's a lot of preclinical progress but bringing it to the clinic is difficult. The translation of nanomedicines from research to clinical application is still hindered by manufacturing reproducibility, scale-up, sterilization, long-term stability, batch consistency, regulatory classification and reliable safety evaluation (11). The therapeutic prediction is further complicated by the variability between experimental models and human biological responses (12). However, the increasing number of clinically studied and approved nanomedicines shows the potential of these systems in cancer, infectious disease, gene delivery and precision therapy (13).

The purpose of this study is to consider nanotechnology-based drug delivery systems from an integrated perspective of biochemical interactions, microbial reaction, and application-oriented performance. It covers metal-oxide nanotoxicity, antimicrobial activity of silver-nanoparticles and comparative PLGA–liposome formulation characteristics. The aims are, identification of toxic physicochemical phenomena, evaluation of toxicity differences with microbial systems in the context of the use of nanoparticles as carrier systems, comparison of the most relevant carrier systems, study of formulation parameters relevant to controlled release, barrier

transport, biocompatibility, therapeutic activity and future clinical translation.

2. METHODOLOGY

2.1 Study Design and Analytical Framework

This multi-source data-integration approach was retrospective, with an aim to examine three complementary aspects of nanotechnology-based drug delivery systems: physicochemical and biochemical interactions, microbial responses and the potential for use in preclinical applications.

The harmonized dataset included 1000 records with 52 harmonized variables, including 394 NanoTox observations, 318 minimum inhibitory concentration (MIC) records for the silver nanoparticles, 288 records for synthetic PLGA or liposome formulations. Each record captured data about the source of the dataset, the type of evidence, the authenticity and the domain of application. Observed data were separated into experimental and literature-curated to avoid interpreting simulated results as lab or clinical data.

2.2 Data Sources

The curated dataset was created by combining three interrelated datasets. The NanoTox dataset provided physicochemical characteristics and toxicity outcomes, such as particle size, hydrodynamic diameter, surface charge, surface area, exposure duration, dosage, and binary toxicity classification of metal-oxide nanoparticles (14).

The data for drug-delivery formulation was taken from a synthetic dataset of PLGA nanoparticles and liposomes for applications in brain cancer (15). This source supplied data on the type of nanocarbons, on the category of the payload, on the targeting strategy, on the physical and chemical properties, on the encapsulation efficiency, on the drug loading, on the release profile, on transport across the blood–brain barrier, on cellular uptake, on biocompatibility, on tumour cytotoxicity, and on off-target toxicity. These observations were not considered experimental or clinical evidence, but rather “data” from a simulation of preclinical data.

Microbial-response data was extracted from NanoAntimicrobialDB, the component of minimum inhibitory concentration for silver-nanoparticles (16). It features literature-curated information about nanoparticle synthesis, size, morphology, bacterial species, Gram classification, experimental condition and MIC values.

2.3 Data Cleaning, Harmonization, and Selection

All variables were scaled to common parameters such as nanomaterial/carrier type, preparation method, morphology, particle size, zeta potential, exposure time, dose, toxicity outcome, MIC, and preclinical performance indicator. Reported values were kept where measurements were original and similar numerical values were converted to standardized measurements. Two observations from the same NanoTox were not considered to be duplicates and were excluded from the total, thus creating 394 unique observations.

All 318 individual records of antimicrobials were included, including microbial species, particle size, MIC and publication data. The number of synthetic records was reduced to 288 "high plausibility" records with complete key variables, conservative particle-size and polydispersity ranges, a balanced representation of PLGA and liposome formulations, and acceptable off-target-toxicity values. The three sources were not row-matched, but united as a harmonised collection as there was no common formulation or experiment identifier. Structural missing values resulting from variables in the source were not imputed.

2.4 Statistical Analysis

Continuous variables were expressed in terms of mean, standard deviation, median and interquartile range and categorical variables frequencies and percentages. Spearman correlation was conducted to analyze the relationship between particle size, surface charge, dose, toxicity, MIC, encapsulation efficiency, BBB transport and biological-response indicators.

Two-group comparisons were done using the Mann–Whitney U test, and variables with more than two groups were analyzed with the Kruskal–Wallis test and corrected post hoc comparisons. Regression and tree based predictive models were used only within source compatible subsets. The partitioning of the train–test samples was group aware or stratified to avoid formulation and source leakage. $p < .05$ was used as the criterion for statistical significance and effect size and confidence intervals are reported. No patient-level efficacy or safety claims were made and clinical interpretation was limited to preclinical relevance and translational potential.

2.5 Data Availability, Ethics, and Licence

The study was secondary, literature-curated, de-identified, or simulated data, and no human participants and/or animals were directly recruited for this study. For each observation a data provenance and authenticity label were kept. The curated dataset and associated metadata are available for sharing and adaptation under the Creative Commons Attribution 4.0 International licence. This allows users to share and adapt the dataset, provided they acknowledge the original datasets, cite the source and disclose any modifications. The synthetic nature of the PLGA and liposome part should be well indicated.

3. RESULTS

3.1 Dataset Composition and Evidence Coverage

A carefully selected analytical data set consisted of 1,000 records in biochemical nanotoxicity, microbial response, and drug-delivery formulation areas. A total of 394 records (39.4%) were the biochemical component, 318 records (31.8%) were the microbial-response component, and 288 records (28.8%) were the drug-delivery component. There were 712 records (71.2%) that were experimental and/or literature curated to be authentic, and 288 records (28.8%) that were high-plausibility simulated PLGA/liposome formulations.

The biochemical subset included five metal-oxide nanotechnology materials, and the microbial subset 148 bacterial strain or species labels. The formulation subset consisted of PLGA carriers and liposome carriers, 144 observations were collected for each family of carriers. Table 1 lists the various data sets in the nanotoxicity,

microbial response, and drug-delivery formulation domains, with a total of 1,000 records. The proportions of records in the three analytical domains are illustrated in Figure 1.

Table 1. Composition and analytical role of the curated dataset

Analytical domain	Data category	Records, n	Dataset share	Evidence status	Primary outcomes
Biochemical interactions	Metal-oxide nanotoxicity	394	39.4%	Authentic curated	Toxicity, particle size, charge and dose
Microbial responses	Silver-nanoparticle MIC	318	31.8%	Authentic literature-curated	MIC, bacterial identity and Gram classification
Drug-delivery applications	PLGA and liposome formulations	288	28.8%	High-plausibility simulated	Encapsulation, BBB transport, uptake and safety
Total	Integrated analytical dataset	1,000	100.0%	Mixed evidence	Cross-domain interpretation

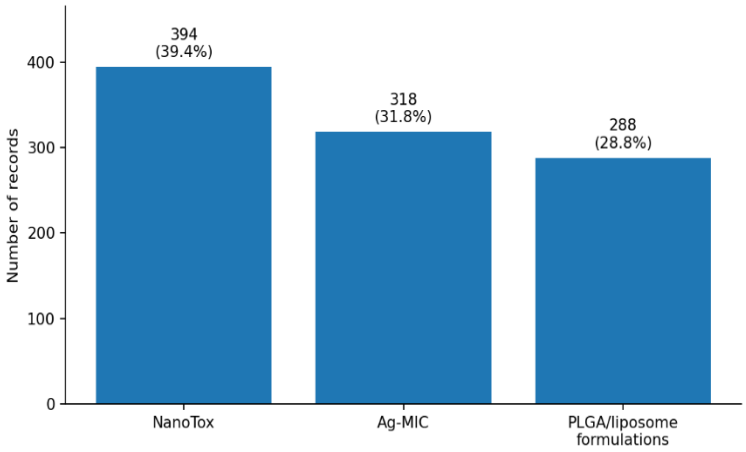

Figure 1. Distribution of observations across the three analytical domains

3.2 Biochemical Interactions and Nanotoxicity

Of the 394 observations of metal-oxide nanoparticles, 98 (24.9%) were considered toxic. There was significant difference in the frequency of toxicity of nanomaterials calculated as $\chi^2 = 93.00$, $p < .001$. The highest percentage of toxic observations was for CuO (70.3%) followed by ZnO (34.3%). The percentage of toxic observations in each sample were: TiO_2 = 3.3%, Al_2O_3 = 0%, Fe_2O_3 = 0%. These results suggest that the composition of the nanomaterials was one of the most important factors influencing their biochemical safety profile. The highest toxicity frequencies were obtained for CuO and ZnO, whereas none of the observations were toxic for Al_2O_3 and Fe_2O_3 as shown in Table 2. As seen in Figure 2, there was a significant difference in toxicity between metal-oxide nanoparticles, with CuO having the highest toxic proportion.

Table 2. Material-specific nanotoxicity profiles

Nanomaterial	n	Toxic, n (%)	Median particle size (nm)	Median zeta potential (mV)	Median dose
Al_2O_3	18	0 (0.0%)	39.7	36.3	5.0
CuO	37	26 (70.3%)	46.3	31.3	25.0
Fe_2O_3	18	0 (0.0%)	42.5	−8.2	5.0
TiO_2	123	4 (3.3%)	25.0	−12.1	20.0
ZnO	198	68 (34.3%)	52.0	21.6	12.5

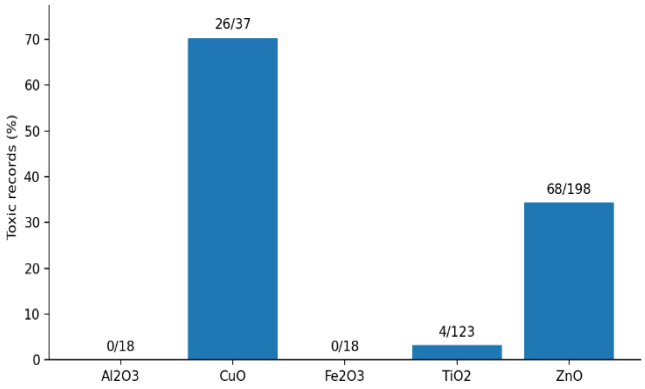

Figure 2. Proportion and number of toxic observations within each metal-oxide nanomaterial

The median (50th percentile) primary particle size of toxic observations was larger than that of non-toxic observations: 52.0 nm and 39.7 nm, respectively. The median zeta potential of the toxic records was also more positive, and the median dose was four times higher. The highest separation between the toxic and non toxic observations was observed for dose (rnbiserial = 0.542).

Toxic records were also associated with lower surface area and longer exposure-time distributions. The five assessed physicochemical or exposure related characteristics were significantly different in the toxicity groups. Table 3 indicates that toxic nanoparticles were larger, more positively charged, had lower surface area, a longer exposure, and higher dose than non-toxic nanoparticles.

Table 3. Physicochemical characteristics according to toxicity classification

Characteristic	Non-toxic, median (IQR), n = 296	Toxic, median (IQR), n = 98	p value	Rank-biserial effect
Particle size (nm)	39.7 (25.0–54.0)	52.0 (45.3–100.0)	<.001	0.324
Zeta potential (mV)	−10.7 (−11.7–27.4)	21.6 (−11.3–31.3)	<.001	0.254
Surface area	40.0 (20.0–66.0)	20.0 (14.5–27.9)	<.001	−0.437
Exposure time (h)	24.0 (12.0–24.0)	24.0 (24.0–42.0)	<.001	0.289
Dose	10.0 (1.0–30.0)	40.0 (25.0–50.0)	<.001	0.542

3.3 Microbial Responses to Silver Nanoparticles

There were 178 Gram-negative and 140 Gram-positive observations in the microbial-response subset. The median MICs of the Gram-negative and Gram-positive bacteria were 18.0 and 14.5 µg/mL, respectively. There is no significant difference in the MIC distributions between Gram classification (Mann–Whitney p = .517).

There is significant variation in the susceptibility levels of the bacteria, as shown by the wide and overlapping MIC ranges. The MIC distribution for Gram-positive and Gram-negative bacteria were similar, and there was considerable variation within each group (Table 4). The MIC values of Gram-positive bacteria and Gram-negatives are highly overlapping as presented in Figure 3.

Table 4. Microbial-response profile according to Gram classification

Gram classification	n	MIC, median (IQR), µg/mL	Particle size, median (IQR), nm	MIC range, µg/mL
Gram-negative	178	18.0 (5.0–64.8)	20.0 (12.6–35.0)	0.11–900
Gram-positive	140	14.5 (6.2–70.0)	20.3 (12.2–35.0)	0.11–1,200

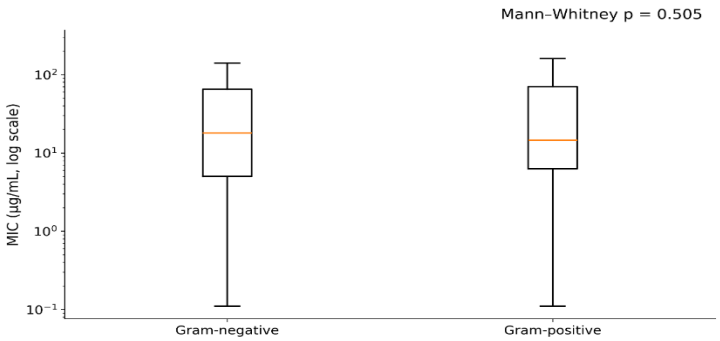

Figure 3. Distribution of silver-nanoparticle minimum inhibitory concentrations for Gram-negative and Gram-positive bacteria

The particle size was weakly positively correlated with the MIC (Spearman's ρ = 0.188, p < .001). So, bigger particle size led to moderately more particle concentrations needed for microbial inhibition. As seen from the small correlation value, the variation in the antimicrobial properties was mostly explained by the particle size. The major categories of preparation or source of the nanoparticles showed significant differences among the MIC values, H (Kruskal–Wallis) = 46.60, p < .001. Nanoparticles manufactured and processed by physical method showed the lowest median level of MIC (4.5 µg/mL). The median MIC of materials from one commercial source was 5.0 µg/mL while the green synthesized nanoparticles had a median of 10.0 µg/mL. The median MIC value was the highest for the chemical reduction preparations (50.0 µg/mL). Variations in particle size, surface chemistry, stabilizing agents and experimental conditions could account for the differences between preparation categories. As presented in Table 5, MIC values obtained by physical and green-synthesis methods were lower than those obtained by chemical-reduction methods. As seen in Figure 4, preparation method of nanoparticles had a significant effect on antimicrobial activity.

Table 5. MIC according to major preparation or source category

Preparation or source category	n	MIC, median (IQR), µg/mL	Median particle size (nm)
Physical method	16	4.5 (2.8–6.6)	12.1
Commercial source—US RNM	25	5.0 (5.0–10.0)	11.2
Green synthesis	117	10.0 (3.1–60.0)	23.0
Commercial source—Nano Nasb	12	40.0 (34.0–40.0)	16.0
Chemical reduction	130	50.0 (10.5–100.0)	30.0

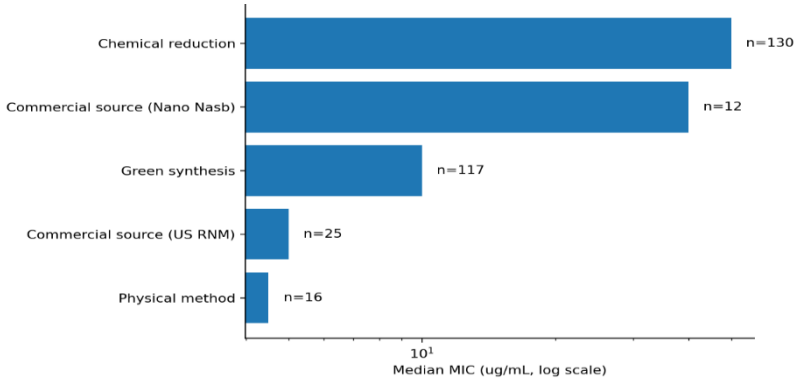

Figure 4. Median MIC across preparation or commercial-source categories represented by at least 10 observations

3.4 Drug-Delivery Performance and Preclinical Application Indicators

A total of 144 PLGA and 144 liposome formulations were included in the drug delivery subset. The mean particle size of liposomes was significantly lower than that of PLGA formulations (136.4 ± 17.2 nm vs. 155.8 ± 19.4 nm). The mean polydispersity index of liposomes was also found to be lower and the mean EE for liposomes was higher.

The stability score and biodegradation score of PLGA formulations were significantly higher. On the other hand, liposomes had higher scores for BBB transport and overall performance. There were no statistically significant differences found in biocompatibility, tumour cytotoxicity or off-target toxicity between the different carrier levels. Table 6 indicates liposomes were better encapsulated and transported across the BBB while PLGA was more stable and biodegradable. Complementary performance profiles of PLGA and liposome formulations across key delivery parameters are illustrated in Figure 5.

Table 6. Comparison of PLGA and liposome formulation characteristics

Characteristic	PLGA, mean ± SD	Liposome, mean ± SD	p value	Higher group
Particle size (nm)	155.8 ± 19.4	136.4 ± 17.2	<.001	PLGA
Polydispersity index	0.21 ± 0.04	0.18 ± 0.03	<.001	PLGA
Encapsulation efficiency (%)	66.9 ± 14.7	74.4 ± 7.5	<.001	Liposome
Stability score	81.7 ± 7.3	79.1 ± 6.6	.004	PLGA
Biodegradation score	79.5 ± 5.7	64.6 ± 5.4	<.001	PLGA
BBB transport score	86.9 ± 7.2	90.8 ± 4.7	<.001	Liposome
Biocompatibility score	91.1 ± 5.8	92.0 ± 4.9	.270	No significant difference
Tumour cytotoxicity score	78.1 ± 6.7	79.4 ± 5.4	.118	No significant difference
Off-target toxicity score	24.2 ± 7.7	24.3 ± 6.9	.742	No significant difference
Overall performance score	83.2 ± 5.4	85.0 ± 2.7	<.001	Liposome

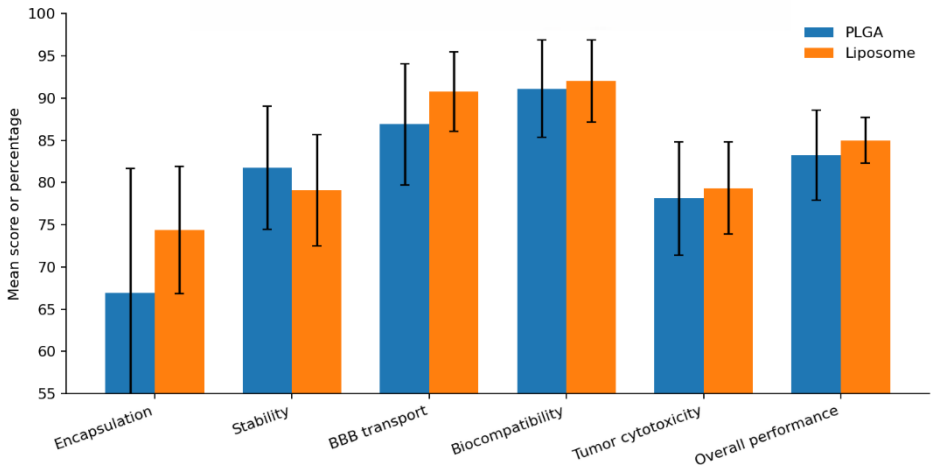

Figure 5. Comparative mean performance indicators for PLGA and liposome formulations. Error bars represent standard deviations

There was a strong association between release-profile distributions and carrier type, $\chi^2 = 92.71$, $p < .001$. Of the PLGA formulations, 61 were biphasic-sustained release and 49 were diffusion-controlled release 34 were erosion-accelerated release. None of the PLGA formulations were considered to be burst-dominated.

In the liposomes, there were 75 biphasic sustainable release, 47 were dominated by burst release and 22 were diffusion controlled. None of the liposomes were termed as erosion-accelerated.

These patterns suggest different release mechanisms of polymeric and lipid based carrier architectures. There was a strong correlation between drug loading and encapsulation efficiency ($\rho = 0.667$, $p < .001$). The performance of BBB transport was positively related to the cellular uptake, tumour-directed cytotoxicity and performance of the formulation.

Specifically, BBB transport correlated with:

- cellular uptake: $\rho = 0.244$, $p < .001$;
- tumour cytotoxicity: $\rho = 0.291$, $p < .001$;
- overall performance: $\rho = 0.424$, $p < .001$.

Biocompatibility was negatively correlated with off-target toxicity ($\rho = -0.597$, $p < .001$). Therefore, formulations that were predicted to have greater non-target toxicity results always showed less compatibility. There is a positive correlation between BBB transport and directed cytotoxicity (Figure 6).

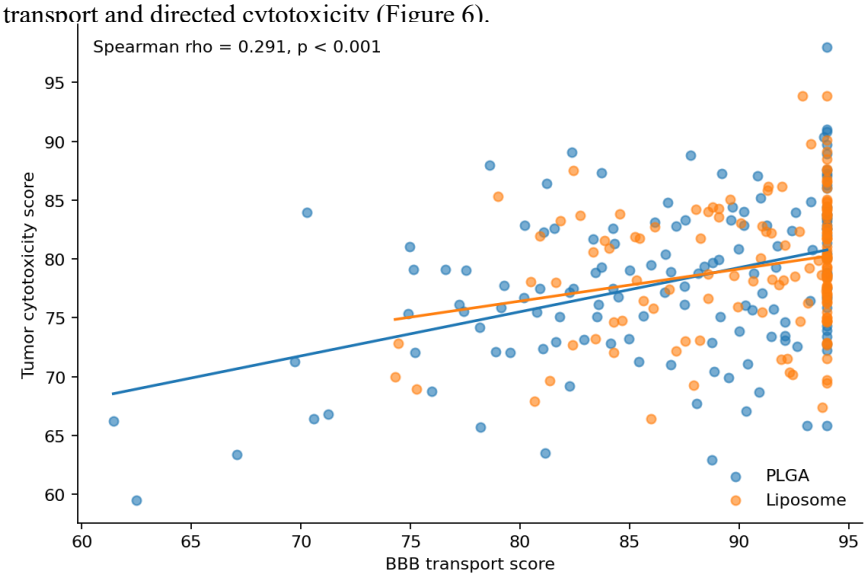

Figure 6. Association between BBB transport and tumour-directed cytotoxicity in PLGA and liposome formulations

3.5 Integrated Findings and Clinical Relevance

The pattern across the three analytical areas was consistent in terms of multiple criteria. Biochemical toxicity was related to the composition of the nanoparticles, their surface charge and primary particle size. Silver nanoparticles with smaller size and specific preparation methods correlated with decreased MIC values in the microbial subset. For the drug delivery subset, the drug to carrier ratio, encapsulation efficiency, release profile, biodegradation, BBB transport and overall performance were all affected by the architecture of the carrier. None of the single physicochemical parameters achieved the best results for all of the measured parameters. For instance, a smaller particle size was linked to an enhanced antimicrobial activity and liposomal formulations had this property, while

biochemical toxicity was also strongly affected by material composition and surface charge and dose. In the same way, higher BBB transport was correlated with better tumour-directed activity, but high performance was only achieved when all the following parameters were controlled simultaneously: encapsulation, cellular uptake, release behavior, biocompatibility and off-target toxicity. The liposome formulations showed improvements in particle-size uniformity, encapsulation efficiency and BBB transport as well as overall performance. PLGA formulations exhibited better stability and biodegradation characteristics. Both carrier families showed similar biocompatibility and tumour cytotoxicity and off-target toxicity scores, suggesting that neither family was generally superior. Patient-level outcomes, endpoints of clinical trials, pharmacokinetic parameters and adverse-event data were not recorded in the data set. Thus, the clinical application findings are a prelude and proxy for clinical effectiveness. As long as this, the integrated results support a staged development approach that allows the assessment of biochemical safety, microbial activity, formulation efficiency, barrier transport and non-target effects together, in order to advance nanotechnology-based drug delivery systems to in vivo or clinical testing.

4. DISCUSSION

The results show that the drug delivery performance of nanotechnology can be influenced by the combination of material composition, particle size, biological environment, dose, and carrier architecture. Chemical identity still plays a central role in nanobio responses with higher toxicity seen for CuO and ZnO, despite the fact that they have similar dimensions (1). The toxicity is associated with bigger particle size, positive zeta potential, long exposure and high dose, which reveals that a multivariable approach could be used for nanosafety assessment (17). Surface charge may have an effect on adsorptions, internalization and stress in cells (5).

The protein corona can also modify the biological identity, behavior in circulation and content delivery. Thus, optimization of nanoparticles should take into account both intrinsic physicochemical properties and acquired biological interfaces (4). The correlation between the particle properties and toxicity observed also demonstrates the significance of precision engineering (18). Tissue-selective formulations can potentially lower systemic exposure and allow for therapeutic activity (19). The recognition and biological compatibility can be enhanced using biomimetic coatings (20). But the successful delivery of the tumour still relies on vascular transport, extravasation and tissue penetration (6). Such limitations are significant to consider why no single particle descriptor could always predict all outcomes and why it is important to use integrated formulation design (21).

The results of the microbial analysis revealed wide overlapping MICs of Gram positive and Gram negative bacteria, and the Gram classification alone did not account for susceptibility. The antibacterial activity of silver nanoparticles is attributed to the disruption of the cell membrane, ion release, induction of oxidative stress and damage to cell proteins and DNA (8). Thus, their activity is not only controlled by a single taxonomic trait, but by the properties of nanoparticles and the microorganisms themselves (7). Therapy with nanomaterials is especially relevant in the fight against resistant pathogens. The positive correlation between particle size and MIC indicates that as particle size decreases, the antimicrobial activity may increase, possibly due to increased surface reactivity (22). However, the weak correlation suggests that morphology, coatings, synthesis residues and analysis conditions also play a significant role. The preparation method played a significant role in determining MIC, which aligns with the findings that nanoparticle synthesis can impact antimicrobial activity (23).

The physical or green-synthesis method can potentially produce desirable size distributions or surface chemistries while the chemical reduction can potentially add stabilizers that alter microbial interaction (24). Surface modification can enhance antibiotic loading, targeting of microbes, and activity against resistant organisms (25). Local exposure to antimicrobial agents can be extended in the case of polymeric nanoparticles (26). The flexible structures also allow for combination therapy and stimulus responsive release (27). The antimicrobial peptide delivery has been equally reported to give benefits. The multifunctional nanocarriers can also have direct antimicrobial, and controlled drug release properties (28). The presence of extracellular matrices in biofilms makes penetration by drugs difficult and allows for persisting infections (9), especially for these applications. In PLGA systems, the anti-biofilm effect and the exposure to the drug can be enhanced (10). They have the potential of addressing various infection types.

The sustained release of antibiotics from PLGA formulations can extend their activity against resistant bacteria (29). Similarly, nisin loaded PLGA nanoparticles have been shown to have an antibiofilm effect (30,30). However, for clinical development of silver nanomaterials, there is a need for standardization of assessment of characterization, dosage and safety. In the drug-delivery subset, liposomes were found to be smaller, less polydispersed, more encapsulated, and to have better BBB transport. The results here are in line with the versatility of lipid nanoparticles (2). Among the available parameters, ionizable lipids and compositional tuning can increase the payload retention and biological transport (31). From traditional liposomes to advanced lipid nanoparticles, their therapy versatility has increased (32). Successful delivery systems for nucleic acids (33) have enhanced their clinical maturity. PLGA formulations, on the other hand, showed better stability and biodegradability, which is suitable for sustained delivery (3). The different release profiles found in the two types of carriers, lipid and polymeric, are basic differences (34). Enhanced BBB transport correlates with tumour cytotoxicity, which is indicative of targeted brain delivery strategies (35). But the moderate values suggest uptake, release, encapsulation and safety are still key determinants (36). The same multi-dimensional argument can be extended to lipid–mRNA cancer systems (37). Thus, there is no universal superiority of PLGA or liposomes (13). Reproducible manufacturing of the product, validated models, scalable manufacturing with the aim of producing a suitable formulation for each

indication will be necessary for clinical translation (11). The biggest challenges are batch variability, regulatory uncertainty, and lack of correspondence between the preclinical models and patients (38). Characterization of the disease and clinically relevant endpoints are still needed (12). These data should thus be considered as preliminary and exploratory, and not as proof of clinical effectiveness.

5. CONCLUSION

The use of NDTDS is shown to have significant potential for enhanced therapeutic delivery, antimicrobial activity, and application-specific properties. All the integrated results show that nanoparticle behavior is a result of interactions between the material composition, particle size, surface charge, surface area, dose, exposure condition, synthesis method and carrier architecture. The toxicity of metal-oxide nanoparticles was found to change dramatically depending on the type of metal oxide nanoparticles, as was observed through biochemical analysis, with CuO and ZnO being more toxic than the other materials that were analyzed. Larger particle size, higher surface charge, longer exposure time, and higher doses were also correlated with toxicity, highlighting the fact that no single physicochemical parameter can be used to assess nanosafety. The microbial-response analysis revealed that the sensitivity to the antibacterial agents could not be fully accounted for by Gram classification. The silver-nanoparticle activity was more strongly affected by their size and the way they were made, their surface properties and experimental conditions. Lower MIC values were typically found for smaller particles and with some physical or green-synthesis methods, further highlighting the need to control the production of nanoparticles for antimicrobial use. The complementary properties of PLGA and liposome formulations were noted when compared to each other. While liposomes had the benefits of uniform particle size, high encapsulation efficiency, BBB transport and overall performance, PLGA formulations possessed a higher degree of stability and biodegradation potential and exhibited sustained release. Both carrier systems were not consistently better, highlighting the need to develop formulations for indications. In general, the study validates the multi-criteria approach to the development of nanomedicine, where all the aforementioned parameters are assessed simultaneously. As the formulation data were preclinical and partially simulated, the results should be viewed as hypothesis generating. Therapeutic efficacy and safety must be confirmed in further studies with standardized laboratory experiments, animal models, pharmacokinetic studies and patient level clinical data.

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