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ANALYTICAL METHOD DEVELOPMENT FOR COMPLEX DRUG DELIVERY SYSTEMS: NANOPARTICLES, LIPOSOMES, AND NANOSPONGES

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ARTICLE HISTORY	ABSTRACT
Received on: 19-02-2026 Revised on: 26-03-2026 Accepted on: 03-05-2026	<p>Nanotechnology-based drug delivery systems (NDDS), including nanoparticles, liposomes, and nanosponges, have significantly transformed modern pharmaceutical research by addressing the limitations of conventional drug delivery approaches. These systems enhance drug solubility, stability, bioavailability, and targeted delivery, thereby improving therapeutic outcomes. However, their complex structure and multi-component nature necessitate the development of robust and reliable analytical methods for effective characterisation. This review focuses on analytical method development strategies for NDDS, emphasising critical quality attributes such as particle size, zeta potential, drug loading, morphology, drug release, and stability. Various analytical techniques, including physicochemical, spectroscopic, chromatographic, thermal, and advanced imaging methods, are discussed for comprehensive characterisation. The review also highlights challenges associated with analytical method development, including system complexity, separation difficulties, stability issues, and reproducibility concerns. A comparative analysis of nanoparticles, liposomes, and nanosponges is presented to illustrate their distinct properties and analytical requirements. Furthermore, regulatory considerations and validation parameters based on ICH guidelines are addressed. Finally, emerging trends such as real-time monitoring tools and personalised nanomedicine are explored, providing insights into future advancements in analytical methodologies for complex drug delivery systems.</p> <p>Keywords: <i>Nanoparticles, Liposomes, Nanosponges, Analytical method development, Drug delivery systems, Characterisation, HPLC, NDDS.</i></p>
	
	

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INTRODUCTION

Nanotechnology-based drug delivery systems (NDDS) have emerged as a transformative approach in modern pharmaceutical sciences, offering innovative solutions to overcome the limitations associated with conventional drug delivery methods. NDDS, including nanoparticles, liposomes, and nanosponges, are engineered at the nanoscale (typically 1–1000 nm) to improve the therapeutic efficacy of drugs by enhancing solubility, stability, bioavailability, and targeted delivery. These systems are particularly advantageous for drugs with poor aqueous solubility, rapid degradation, and limited bioavailability, thereby enabling improved pharmacokinetic and pharmacodynamic profiles [1].

In modern pharmaceuticals, the application of NDDS has significantly expanded due to their ability to provide controlled and site-specific drug release, reduce systemic toxicity, and enhance patient compliance. Liposomes, for instance, have been extensively utilized for encapsulating both hydrophilic and lipophilic drugs, enabling targeted delivery to specific tissues. Similarly, polymeric and lipid-based nanoparticles offer sustained release and protection of drugs from enzymatic degradation, while nanosponges provide a porous matrix for controlled drug entrapment and release. These advanced delivery systems have found applications in diverse therapeutic areas, including cancer therapy, infectious diseases, and central nervous system disorders [2,3].

Despite these advantages, the inherent complexity of NDDS presents significant challenges in their characterization and quality assessment. Unlike conventional dosage forms, NDDS are multi-component systems with critical attributes such as particle size, surface charge, morphology, drug loading, and release kinetics, all of which influence their performance.

Therefore, robust and reliable analytical methods are essential to ensure the quality, safety, and efficacy of these formulations throughout their lifecycle, from development to commercialisation [4]. Analytical method development for NDDS requires a comprehensive and systematic approach due to the intricate nature of these systems. Traditional analytical techniques alone are often insufficient, necessitating the integration of advanced physicochemical, spectroscopic, chromatographic, and imaging techniques. The development of stability-indicating methods, capable of distinguishing between free and encapsulated drug as well as degradation products, is particularly critical. Furthermore, method validation in accordance with international regulatory guidelines, such as those outlined by the International Council for Harmonisation (ICH), is essential to ensure accuracy, precision, specificity, and reproducibility [5]. The scope of this review is to provide a comprehensive overview of analytical method development strategies for complex drug delivery systems, with a particular focus on nanoparticles, liposomes, and nanosponges. The review discusses critical quality attributes, various analytical techniques employed for characterization, challenges associated with method development, and regulatory considerations. Additionally, recent advancements and future perspectives in analytical methodologies for NDDS are highlighted to provide insights into ongoing developments in this rapidly evolving field [6].

OVERVIEW OF DRUG DELIVERY SYSTEMS

Nanotechnology-based drug delivery systems (NDDS) have emerged as a powerful approach in pharmaceutical research, enabling improved therapeutic efficacy through enhanced drug solubility, stability, and targeted delivery. These systems operate at the nanoscale and are designed to overcome the limitations of conventional dosage forms, such as poor bioavailability, rapid degradation, and lack of site specificity. Among various NDDS, nanoparticles, liposomes, and nanosponges are widely explored due to their unique physicochemical properties and versatility in drug delivery applications [7,8].

Nanoparticles

Nanoparticles are defined as solid colloidal systems with particle sizes typically ranging from 1 to 1000 nm, in which drugs can be encapsulated, dissolved, or adsorbed onto the surface. These carriers are primarily designed to improve drug delivery efficiency by enhancing solubility and protecting the drug from degradation. Based on their composition, nanoparticles are broadly classified into polymeric nanoparticles and lipid-based nanoparticles. Polymeric nanoparticles are prepared using biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and chitosan, allowing controlled drug release and improved stability. In contrast, lipid-based nanoparticles, including solid lipid nanoparticles and nanostructured lipid carriers, offer better biocompatibility and are particularly suitable for lipophilic drugs [9].

The advantages of nanoparticles include improved bioavailability, controlled and sustained drug release, targeted delivery to specific tissues, and reduced systemic toxicity. Additionally, nanoparticles can enhance cellular uptake and protect against enzymatic degradation, making them highly

suitable for the delivery of sensitive therapeutic agents such as proteins and nucleic acids [10].

Table 1: Applications of Nanoparticles in Drug Delivery

Drug Delivery System	Application Area	Example Drug/Formulation
Nanoparticles	Cancer therapy	Paclitaxel-loaded PLGA nanoparticles
	Oral drug delivery	Curcumin nanoparticles
	Brain delivery	Rivastigmine nanoparticles
	Protein/peptide delivery	Insulin-loaded nanoparticles
	Gene delivery	siRNA nanoparticles
	Antimicrobial therapy	Ciprofloxacin nanoparticles
	Vaccine delivery	Antigen-loaded nanoparticles
	Ocular delivery	Timolol nanoparticles
	Transdermal delivery	Diclofenac nanoparticles
	Controlled release systems	Ibuprofen nanoparticles

Liposomes

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. Due to their structural similarity to biological membranes, liposomes exhibit excellent biocompatibility and low toxicity. The amphiphilic nature of phospholipids enables liposomes to encapsulate both hydrophilic drugs within the aqueous core and lipophilic drugs within the lipid bilayer. This dual drug-loading capability makes liposomes versatile carriers for a wide range of pharmaceutical compounds [11].

Liposomes have been extensively utilised in various therapeutic applications, particularly in targeted drug delivery for cancer treatment, where they help reduce systemic toxicity and improve drug accumulation at the tumour site. They are also widely used in vaccine delivery, gene therapy, and the treatment of infectious and inflammatory diseases. Furthermore, liposomal formulations have shown significant potential in enhancing drug stability and prolonging circulation time in the body [12].

Table 2: Applications of Liposomes in Drug Delivery

Drug Delivery System	Application Area	Example Drug/Formulation
Liposomes	Cancer therapy	Doxorubicin liposomes (Doxil)
	Vaccine delivery	mRNA COVID-19 vaccines
	Gene therapy	Liposomal gene carriers
	Antifungal therapy	Amphotericin B liposomes
	Ophthalmic delivery	Ciprofloxacin liposomes
	Pulmonary	Salbutamol liposomes

	delivery	
	Dermal delivery	Clotrimazole liposomes
	Anti-inflammatory therapy	Diclofenac liposomes
	Antiviral therapy	Acyclovir liposomes
	Targeted delivery	PEGylated liposomes

Nanosponges

Nanosponges are nanoscale, porous drug delivery systems characterized by a three-dimensional network structure capable of encapsulating both hydrophilic and hydrophobic drugs. These systems are commonly synthesized using cyclodextrins cross-linked with suitable agents, forming a stable and highly porous matrix. Cyclodextrins possess a hydrophobic internal cavity and a hydrophilic outer surface, enabling the formation of inclusion complexes with various drug molecules, thereby improving solubility and stability. The unique porous structure of nanosponges allows for controlled and sustained drug release, protecting the drug from environmental degradation such as heat, light, and oxidation. Additionally, nanosponges offer versatility in formulation, as they can be incorporated into oral, topical, and parenteral dosage forms. Their ability to enhance drug stability, reduce dosing frequency, and improve patient compliance makes them a promising platform in advanced drug delivery systems [13].

Table 3: Applications of Nanosponges in Drug Delivery

Drug Delivery System	Application Area	Example Drug/Formulation
Nanosponges	Solubility enhancement	Itraconazole nanosponges
	Controlled drug release	Dexamethasone nanosponges
	Topical delivery	Ketoconazole nanosponges gel
	Oral delivery	Celecoxib nanosponges
	Anticancer therapy	Camptothecin nanosponges
	Antiviral delivery	Acyclovir nanosponges
	Enzyme stabilization	Enzyme-loaded nanosponges
	Detoxification	Toxin-absorbing nanosponges
	Cosmetic applications	Vitamin C nanosponges
	Oxygen delivery	Oxygen-loaded nanosponges

CRITICAL QUALITY ATTRIBUTES (CQAS)

Critical Quality Attributes (CQAs) are the key physicochemical and functional properties of nanotechnology-based drug delivery systems (NDDS) that must be controlled to ensure product quality, safety, and therapeutic efficacy. For complex

systems such as nanoparticles, liposomes, and nanosponges, CQAs play a crucial role in determining in vivo performance, stability, and reproducibility. A systematic evaluation of these attributes is essential during analytical method development and validation.

Particle Size and Polydispersity Index (PDI)

Particle size is one of the most critical parameters influencing drug distribution, cellular uptake, and biodistribution of NDDS. Typically, nanosystems range from 1 to 1000 nm, and slight variations in size can significantly affect pharmacokinetics and therapeutic outcomes. Smaller particles tend to exhibit enhanced permeability and retention (EPR) effect, particularly in tumor targeting.

The polydispersity index (PDI) provides information about the uniformity of particle size distribution. A PDI value less than 0.3 generally indicates a homogeneous system, whereas higher values suggest aggregation or heterogeneity. Therefore, precise control of particle size and PDI is essential to ensure consistency and predictable drug release behaviour [14,15].

Zeta Potential

Zeta potential is a measure of the surface charge of nanoparticles and plays a vital role in determining colloidal stability. It reflects the electrostatic repulsion between particles, which prevents aggregation. Typically, a zeta potential value greater than +30 mV or less than -30 mV indicates good stability of the nanosystem.

In addition to stability, zeta potential also influences biological interactions such as cellular uptake, protein binding, and circulation time. Positively charged particles may exhibit enhanced cellular uptake, while negatively charged or neutral systems may demonstrate improved circulation stability.[16]

Drug Loading and Entrapment Efficiency

Drug loading refers to the amount of drug incorporated into the nanocarrier relative to the total weight of the formulation, while entrapment efficiency indicates the percentage of drug successfully encapsulated within the system. These parameters are critical in determining the therapeutic effectiveness and dosing requirements of NDDS.

High drug loading and entrapment efficiency are desirable as they reduce the amount of carrier material required and improve drug delivery efficiency. However, these parameters depend on several factors, including the physicochemical properties of the drug, formulation composition, and preparation method [17,18].

Morphology

Morphology refers to the shape and surface characteristics of the nanocarriers, which can significantly influence drug release, cellular uptake, and biodistribution. Nanoparticles may exhibit spherical, rod-shaped, or irregular structures, while liposomes typically appear as spherical vesicles and nanosponges as porous networks. Advanced imaging techniques such as scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are commonly used to evaluate morphology. Uniform and well-defined morphology is essential for ensuring reproducibility and stability of the formulation [19].

Drug Release Profile

The drug release profile describes the rate and mechanism by which the drug is released from the carrier system. Controlled

and sustained release is often desirable to maintain therapeutic drug levels over an extended period and reduce dosing frequency.

Drug release from NDDS may occur through diffusion, erosion, swelling, or a combination of these mechanisms. In vitro release studies are typically conducted using dialysis methods or dissolution testing to simulate physiological conditions. A well-characterised release profile is essential for predicting in vivo performance [20].

Stability

Stability is a critical attribute that determines the shelf life and performance of NDDS under various environmental conditions. It includes physical stability (particle size, aggregation), chemical stability (drug degradation), and biological stability (interaction with biological components).

Factors such as temperature, pH, light exposure, and storage conditions can significantly affect stability. Therefore, stability studies must be conducted according to regulatory guidelines to ensure that the formulation maintains its integrity, efficacy, and safety throughout its intended shelf life [21].

Analytical Method Development Strategy

Analytical method development for complex drug delivery systems such as nanoparticles, liposomes, and nanosponges requires a systematic and scientific approach to ensure accurate, reliable, and reproducible results. Due to the multi-component nature and nanoscale characteristics of these systems, method development must consider both the physicochemical properties of the drug and the carrier system. A well-designed analytical strategy is essential for evaluating critical quality attributes, ensuring product consistency, and meeting regulatory requirements [22].

Selection of Method

The selection of an appropriate analytical method is the first and most critical step in method development. It depends on the nature of the drug, formulation components, and the intended purpose of analysis, such as quantification, characterisation, or stability assessment. For instance, chromatographic techniques like HPLC and UPLC are preferred for drug estimation and impurity profiling, while spectroscopic methods such as FTIR and NMR are used for structural characterization and compatibility studies. Additionally, the method must be sensitive, specific, and capable of distinguishing between free drug, encapsulated drug, and degradation products. The selection process often involves preliminary screening of different analytical techniques to identify the most suitable method based on accuracy, precision, and feasibility.

Sample Preparation Challenges

Sample preparation is a critical step that significantly influences analytical accuracy and reproducibility. In complex drug delivery systems, separating the drug from the carrier matrix without altering its integrity is challenging. For example, distinguishing between free and encapsulated drug requires careful extraction techniques, such as centrifugation, filtration, or solvent extraction. Improper sample preparation may lead to drug leakage, degradation, or aggregation of nanocarriers, resulting in inaccurate results. Therefore, it is essential to develop standardized and reproducible sample preparation protocols that preserve the structural and

chemical integrity of the system while ensuring complete drug recovery.

Method Optimization

Method optimization involves fine-tuning analytical parameters to achieve optimal performance. In chromatographic methods, this includes selection of mobile phase composition, pH, flow rate, column type, and detection wavelength. Similarly, in spectroscopic and physicochemical techniques, parameters such as sample concentration, scanning range, and instrument settings must be carefully adjusted. Optimization aims to improve method sensitivity, resolution, and reproducibility while minimizing analysis time and cost. A systematic approach, often guided by Design of Experiments (DoE), is employed to evaluate the influence of multiple variables and identify optimal conditions. This step ensures that the developed method is robust and suitable for routine analysis [23-25].

Validation Parameters (ICH Q2 Guidelines)

Method validation is performed to demonstrate that the analytical method is suitable for its intended purpose, as per International Council for Harmonisation (ICH) Q2 guidelines. Key validation parameters include [26]:

- Accuracy: Closeness of measured value to the true value
- Precision: Repeatability and reproducibility of the method
- Specificity: Ability to measure analyte in the presence of impurities and excipients
- Linearity: Proportional relationship between concentration and response
- Range: Interval between upper and lower concentration levels
- Limit of Detection (LOD) and Limit of Quantification (LOQ): Sensitivity of the method
- Robustness: Ability to remain unaffected by small variations in conditions

Validation ensures that the method produces consistent and reliable results and complies with regulatory standards required for pharmaceutical development and quality control.

Comparative Analysis

Nanoparticles, liposomes, and nanosponges differ significantly in structure and functionality, with nanoparticles offering controlled and targeted delivery, liposomes providing excellent biocompatibility and dual drug-loading capacity, and nanosponges enhancing solubility through porous encapsulation. The choice of system and analytical techniques depends on formulation complexity, drug properties, and intended therapeutic application [26-30].

Table 04: Comparison of Nanoparticles, Liposomes, and Nanosponges

Parameter	Nanoparticles	Liposomes	Nanosponges
Structure	Solid colloidal particles (polymeric/lipid)	Phospholipid bilayer vesicles	Porous, 3D cross-linked network
Drug Loading	Encapsulation/adsorption	Hydrophilic (core) & lipophilic (bilayer)	Inclusion in porous cavities

Size Range	1-1000 nm	50-500 nm	<1000 nm
Techniques Used	DLS, Zeta potential, SEM/TEM, HPLC	DLS, TEM, FTIR, HPLC, DSC	FTIR, SEM, DSC, HPLC
Advantages	Controlled release, targeting, high stability	Biocompatible, dual drug loading	Improved solubility, sustained release
Limitations	Possible toxicity, aggregation	Leakage, stability issues	Limited large-scale production
Applications	Cancer, CNS, vaccines	Cancer, gene therapy, vaccines	Oral, topical, solubility enhancement

CHALLENGES IN METHOD DEVELOPMENT

Analytical method development for complex drug delivery systems is associated with several challenges due to their heterogeneous and multi-component nature. One of the primary difficulties lies in the complexity of systems, where multiple components such as drugs, polymer/lipid, and stabilisers, interact, making characterization intricate. This complexity often requires the integration of multiple analytical techniques to obtain comprehensive information. Another significant challenge is related to separation issues, particularly in distinguishing between free drug and encapsulated drug. Conventional analytical methods may fail to accurately quantify these fractions, leading to errors in drug loading and release studies. Advanced separation techniques and careful sample preparation are therefore essential.

Stability problems also pose a major concern, as nanocarriers are highly sensitive to environmental conditions such as temperature, pH, and light. Instability can result in aggregation, drug leakage, or degradation, affecting analytical accuracy and product performance. Furthermore, reproducibility is a critical issue, especially during scale-up. Minor variations in preparation or analytical conditions can significantly impact results, making it difficult to achieve consistent and reliable outcomes. Hence, robust method development and validation are crucial [31,32].

FUTURE PERSPECTIVES

The field of analytical method development for nanotechnology-based drug delivery systems is rapidly evolving, with increasing emphasis on innovation and standardisation. One of the key future needs is the development of standardised analytical protocols, which will enable consistent evaluation and regulatory acceptance of complex nanocarrier systems across different laboratories and industries. Advancements in real-time monitoring tools are expected to play a transformative role in analytical science.

Techniques such as in-line spectroscopy, process analytical technology (PAT), and advanced imaging methods will allow continuous monitoring of formulation parameters, improving quality control and process efficiency. Another promising direction is the emergence of personalized nanomedicine, where drug delivery systems are tailored to individual patient needs. This approach will require highly sensitive and precise analytical methods to ensure accurate dosing, targeting, and therapeutic outcomes.

CONCLUSION

Analytical method development for complex drug delivery systems such as nanoparticles, liposomes, and nanosponges plays a crucial role in ensuring their quality, safety, and therapeutic efficacy. The intricate nature of these systems requires the integration of multiple analytical techniques to comprehensively evaluate critical quality attributes, including particle size, surface charge, drug loading, morphology, release behavior, and stability. Despite significant advancements, challenges such as system complexity, separation of free and encapsulated drug, stability issues, and reproducibility remain critical concerns. A systematic approach involving appropriate method selection, optimization, and validation in accordance with regulatory guidelines is essential for reliable analysis. The growing emphasis on standardization, real-time analytical tools, and advanced imaging techniques is expected to enhance method robustness and efficiency. Furthermore, the emergence of personalized nanomedicine will demand more precise and sensitive analytical methods. Overall, continued innovation in analytical methodologies will be vital for the successful development and commercialization of advanced drug delivery systems.

AUTHOR CONTRIBUTIONS

Kiran Kumar Byram: Conceptualisation, literature review, data curation, writing – original draft preparation, writing – review and editing, and final approval of the manuscript.

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