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REVIEW ARTICLE

Challenges and Strategies in Nanoparticle-Mediated Drug Release: Mechanisms and Future Directions

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Abstract

Nanoparticle drug delivery systems (NPDDS) promise to increase the efficacy and safety of therapeutic agents, yet achieving controlled and sustained release of active ingredients from these nanoparticles remains a significant challenge hindering the full realization of this technology's benefits. This paper aims to uncover the key problems associated with nanoparticle drug release by delving into the fundamental concepts and mechanisms underlying this intricate process. Drug release mechanisms like diffusion, erosion, and stimuli-responsive release are intricately examined, while critically evaluating the obstacles posed by factors such as particle size, surface properties, drug-carrier interactions, and physiological barriers. Some of the effects of not achieving controlled and sustained release are burst release and incomplete release, as well as premature drug release and instability. Future directions and strategies for improved drug release are proposed, including nanoparticle design and engineering, stimuli-responsive nanoparticle, and hybrid nanoparticle systems. By synergistically addressing the key problem of nanoparticle drug release through this comprehensive approach, the full potential of this transformative technology can be unlocked, paving the way for more effective and safer therapeutic interventions, ultimately leading to improved patient outcomes and reduced healthcare costs.

Keywords: Nanoparticle, Drug release, Nanoparticle design-engineering, Stimuli-responsive nanoparticle, Hybrid nanoparticle system

Introduction

The emergence of nanoparticle-based drug delivery systems (NPDDS) has paved the way for overcoming the limitations of conventional drug formulations, offering enhanced pharmacokinetic properties, targeted delivery, and improved therapeutic efficacy [1]. These nanosized carriers, encompassing polymeric nanoparticles, liposomes, and inorganic nanoparticles, possess unique physicochemical characteristics that facilitate the encapsulation and protection of drug molecules while enabling their controlled release at the desired site of action [2].

A pivotal aspect of nanoparticle-based drug delivery is the ability to achieve a controlled and sustained release of the encapsulated therapeutic agent over an extended period. This controlled drug release not only optimizes the therapeutic concentration at the target site but also mitigates systemic exposure and potential adverse effects [3]. However, attaining the desired release kinetics poses a complex challenge,

influenced by various factors such as nanoparticle properties, drug characteristics, and physiological conditions [4].

The significance of controlled drug release from nanoparticles lies in its potential to enhance therapeutic efficacy, improve patient adherence, and reduce toxicity. For instance, sustained release formulations can maintain drug levels within the therapeutic window, minimizing the need for frequent dosing and enhancing patient compliance [5]. Moreover, targeted delivery of drugs to specific tissues or cells can maximize the therapeutic effect while minimizing off-target effects and systemic toxicity [6].

This review aims to provide a comprehensive understanding of the critical challenge of nanoparticle drug release, encompassing the underlying principles, obstacles, and future prospects. It will delve into the mechanisms of drug release from nanoparticles, including diffusion-controlled, degradation-controlled, and stimuli-responsive release processes. Furthermore, the review will critically analyze the challenges associated with achieving the desired drug release profiles, such as burst release, premature drug release, lack of spatiotemporal control, and potential toxicity issues. Additionally, the article will explore innovative strategies and future directions for improving drug release from nanoparticles. This includes the design and engineering of novel nanoparticle architectures, the development of stimuli-responsive systems, the integration of combination and hybrid approaches, and the application of advanced characterization and modelling techniques.

By unravelling the critical challenge of nanoparticle drug release, this review seeks to provide valuable insights and guidance for researchers, pharmaceutical scientists, and clinicians working in the field of nanomedicine and drug delivery. Ultimately, addressing the challenges of controlled drug release from nanoparticles has the potential to revolutionize therapeutic interventions, leading to more efficacious, safer, and personalized treatment approaches.

Mechanism of drug release from nanoparticle

Achieving controlled release of drugs from carriers is vital for keeping medication levels in the bloodstream within the therapeutic range [7]. This allows patients to take fewer doses while still maintaining an effective concentration over time. The ideal scenario is a delivery system that releases the drug at a constant rate, providing a steady supply. However, making this “0-order release” a reality is challenging [7,8]. The composition of the nanocarrier plays a huge role - not just the drug itself, but also the polymer, other ingredients, and their relative amounts. How the carrier is manufactured also impacts drug release behaviour. In general, there are 3 main mechanisms by which drugs can escape from these tiny vehicles: Diffusing out over time, being released as the carrier slowly breaks down, or getting pushed out in response to some external trigger. These different release mechanisms will be deeply discussed shortly. But first, it’s important to understand why controlled release is so desirable from both a patient perspective and a therapeutic standpoint. Fewer doses mean greater convenience and better adherence to the prescribed regimen. And maintaining a consistent level of the drug avoids the peaks and valleys that could lead to toxic side effects or a Window where the medication is ineffective.

Diffusion-controlled release

The diffusion-controlled release mechanism represents one of the fundamental modes by which drug molecules are liberated from NPDDS. In this mechanism, the encapsulated drug molecules disseminate from the nanoparticle matrix via diffusion through pores, channels, or the polymeric network itself, as depicted in **Figure 1**. The kinetics of drug release are governed by the diffusion coefficient of the drug within the nanoparticle matrix, as well as the chemical nature of the bioactive molecules, the nanoparticle composition, and the surrounding environmental conditions [9].

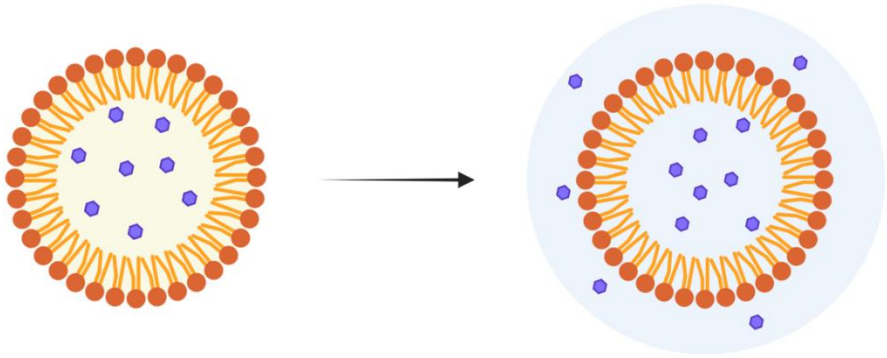

Figure 1 Diffusion-controlled release mechanism of a nanoparticle.

The fundamental concept underpinning diffusion-controlled release is predicated upon Fick's laws of diffusion. These laws elucidate the phenomenon of molecular migration from regions of high concentration to regions of low concentration through the process of diffusion [10]. The first of Fick's law postulates that the rate of diffusion is directly proportional to the concentration gradient between 2 regions (Eq. (1)). The second law (Eq. (2)) delineates the temporal variation of concentration in relation to the diffusion coefficient and the spatial variation in concentration [11]. The diffusion-controlled release process can be further categorized into 3 principal mechanisms: Reservoir or membrane-controlled release, matrix-controlled release, and a combined reservoir-matrix release [12].

$$J = -D\frac{\partial \phi}{\partial x} \quad (1)$$

$$\frac{\partial \phi}{\partial t} = D\frac{\partial^2 \phi}{\partial x^2} \quad (2)$$

where,

J: Diffusive flux $[\mathrm{mol}/(\mathrm{m}^2 \cdot \mathrm{s})]$, representing the amount of substance flowing through a unit area per unit time.

D: Diffusion coefficient $[\mathrm{m}^2/\mathrm{s}]$, a material-specific constant describing how easily a substance diffuses through a medium.

$\frac{\partial \phi}{\partial x}$: Concentration gradient $[\mathrm{mol}/\mathrm{m}^4]$ → The rate of change of concentration (ϕ) with distance (x).

$\frac{\partial^2 \phi}{\partial x^2}$: Second spatial derivative of concentration [mol/m5], representing the curvature of the concentration profile.

In the reservoir or membrane-controlled release mechanism, the drug molecules are encapsulated within a reservoir or core, enveloped by a polymeric membrane. The drug release rate is primarily governed by the diffusion of the drug molecules through this rate-limiting membrane [13]. Conversely, in the matrix-controlled release mechanism, the drug is homogeneously dispersed within a polymeric matrix, and the release kinetics are modulated by the diffusion of the drug through this matrix [14]. The combined reservoir-matrix release mechanism represents a hybrid approach, wherein the drug is partitioned into 2 distinct phases: A reservoir phase and a matrix phase. In this scenario, drug release is mediated by the cumulative contributions of diffusion from the reservoir and the matrix phases [15].

Numerous factors influence the diffusion-controlled release kinetics, including the diffusion coefficient of the drug within the nanoparticle matrix, which is contingent upon the drug's physicochemical properties, such as molecular size, solubility, and lipophilicity [16]. Additionally, the composition and architecture of the nanoparticle matrix, encompassing parameters such as polymer crystallinity, porosity, and degradation rate, exert a significant impact on the drug release profile [17]. Furthermore, environmental conditions, including temperature, pH, and ionic strength, can modulate the diffusion coefficient and consequently alter the drug release kinetics [18].

Reservoir and matrix-controlled release

In diffusion-mediated nanoparticle drug delivery systems (NPDDS), reservoir-controlled and matrix-controlled mechanisms represent 2 fundamentally different architectural approaches. In reservoir-based

systems, the drug payload occupies a central core distinctly encapsulated by a polymeric membrane, creating a clear spatial separation between drug and barrier. Release occurs as drug molecules traverse this outer membrane, with release kinetics primarily governed by membrane permeability, membrane thickness, and the drug's solubility and diffusion coefficient within the membrane material. These parameters create a rate-limiting barrier that enables highly predictable, 0-order release kinetics when properly engineered. These relationships are illustrated in **Figure 2**, which demonstrates how these parameters interact to control the temporal profile of drug release. The membrane effectively functions as a rate-limiting barrier that enables predictable, sustained delivery when properly engineered with appropriate materials and dimensions [13]. This mechanism is commonly observed in nano-capsule or core-shell nanoparticle architectures. The kinetics of drug release can be mathematically described by the Higuchi equation, as presented in Eqs. (3) and (4) [14].

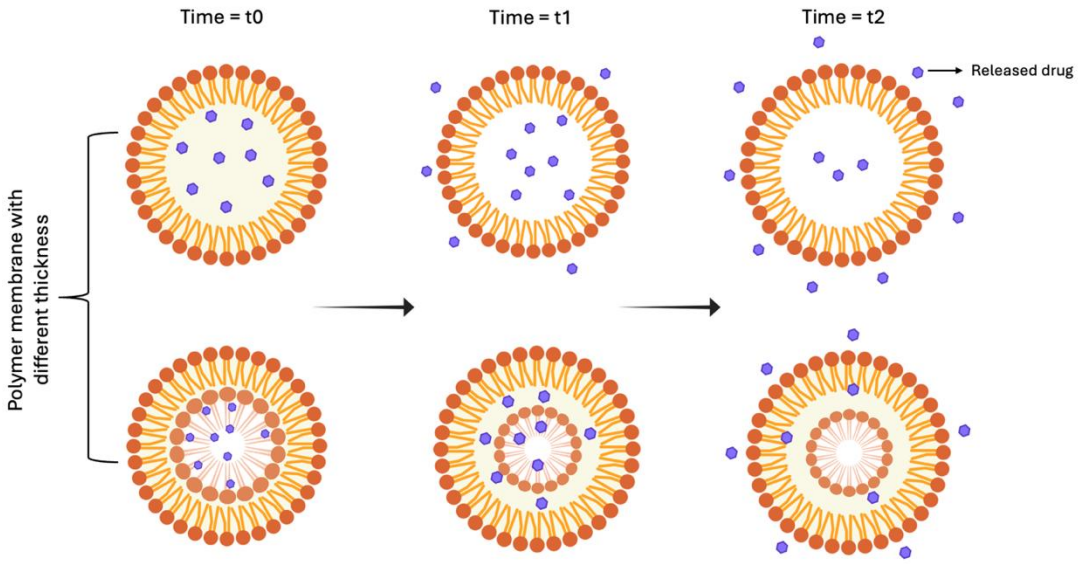

Figure 2 Reservoir/membrane-controlled release mechanism.

$$Q_t = \sqrt{D \cdot (2C_0 - C_s) \cdot C_s \cdot t} \quad (3)$$

$$Q_t = k_H \cdot \sqrt{t} \quad (4)$$

where,

Q_t : Cumulative drug released per unit area (mass/area).

D: Diffusion coefficient of the drug in the matrix (length^2/time).

C_0 : Initial drug concentration in the matrix (mass/volume).

C_s: Drug solubility in the matrix (mass/volume).

t: Time

In contrast, matrix-controlled systems feature active ingredients uniformly dispersed or dissolved throughout a polymer matrix without distinct compartmentalization. This homogeneous distribution means drug molecules must navigate through an increasingly lengthy diffusion path as release progresses, typically resulting in first-order or square-root-of-time release kinetics. While reservoir systems maintain relatively constant release rates due to stable diffusion path lengths, matrix systems exhibit gradually decreasing release rates as the diffusion distance increases for remaining drug molecules. Additionally, matrix systems are more significantly influenced by polymer degradation or erosion characteristics, which can create dynamic changes in diffusion pathways over time [4]. These structural and mechanistic differences, highlight why reservoir systems typically achieve more sustained and constant release profiles, while matrix systems offer simpler fabrication and often greater stability during storage. This approach is commonly used in polymeric nanoparticles made with

biodegradable polymers such as PLGA. Mathematical models like the Korsmeyer-Peppas (Eq. (5)) and Weibull models (Eq. (6)) are often employed to describe and forecast the release kinetics of drugs from these systems [15].

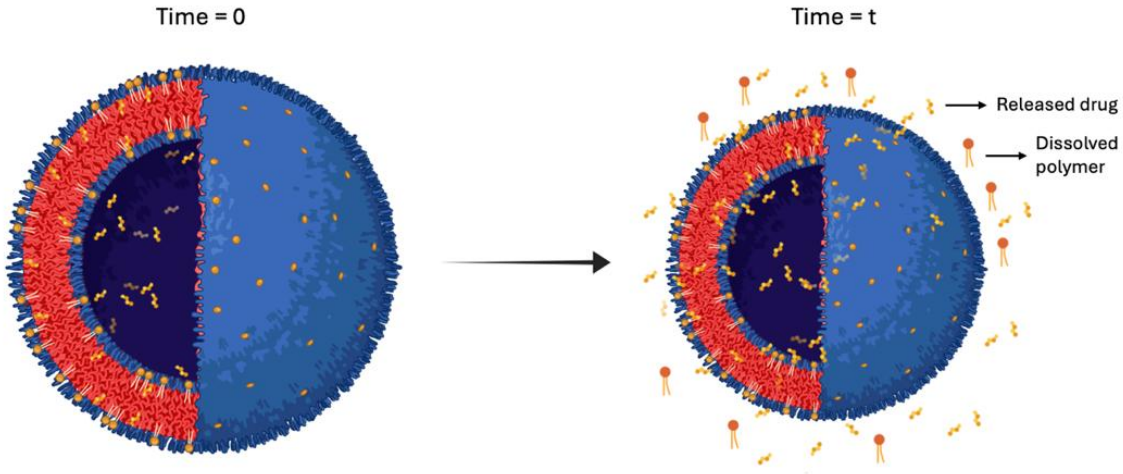

Figure 3 Matrix-controlled release mechanism.

$$\frac{M_t}{M_\infty} = k \cdot t^n \quad (5)$$

$$\frac{M_t}{M_\infty} = 1 - e^{-(t/\alpha)^\beta} \quad (6)$$

where,

$\frac{M_t}{M_\infty}$: Fraction of drug released at time t.

k: Release rate constant (incorporates structural and geometric factors).

n: Diffusional exponent indicating the release mechanism.

α: Scale parameter (related to release rate).

β: Shape parameter (indicates release profile type)

t: Time

Combined reservoir-matrix release

Some nanoparticle systems exhibit a combination of reservoir and matrix-controlled release mechanisms. In this scenario, a portion of the drug is encapsulated within a core or reservoir, while the rest is dispersed throughout the polymer matrix. The overall rate of drug release is influenced by both diffusion mechanisms [2]. Comprehending and controlling the diffusion-driven release mechanism is vital for attaining the intended drug release patterns and therapeutic efficacy in NPDDS. Through meticulous selection of nanoparticle composition, structure, and integration of functional groups or additives capable of interacting with the drug, scientists can customize the diffusion characteristics of the active ingredients within a nanoparticle matrix, thus enhancing and managing drug release kinetics.

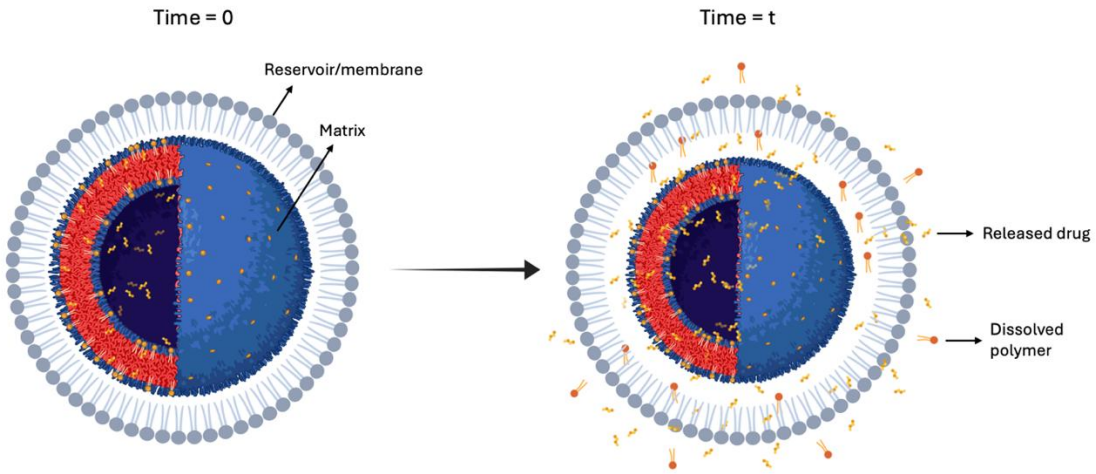

Figure 4 Combined reservoir-matrix release mechanism.

Degradation-controlled release

Degradation-controlled release stands as a pivotal method in drug delivery from NPDDS. Here, drug molecules nestled within the nanoparticle matrix are gradually liberated as the matrix material undergoes degradation or erosion over time (**Figure 5**). As this matrix disintegrates, it facilitates the release of the encapsulated drug molecules [16]. The pace of drug release from the nanoparticles hinges on the rate of degradation of the nanoparticle matrix [17].

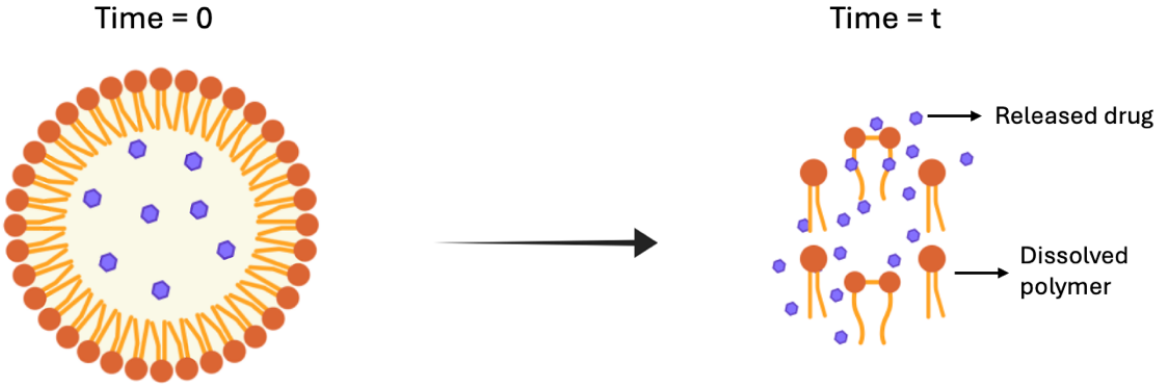

Figure 5 Degradation-controlled release mechanism.

Typically, degradation-based release systems employ biodegradable polymers like polyesters, polyamides, and polysaccharides, which foster drug release through enzymatic degradation, where ester or amide bonds are cleaved, or via induction of hydrolysis [18-20]. The degradation process affects a polymer matrix consisting of materials such as PLGA, PLA, or PCL, resulting in the simultaneous breakdown of the entire matrix. Conversely, matrices fashioned from anhydrides or orthoesters generally erode from the surface towards the center, leading to faster polymer degradation compared to water diffusion into the matrix [21,22]. Nevertheless, in a matrix of reduced size, like those encountered in nanoparticles, the water's diffusion distance is notably brief, and the crystallization area is restricted. This results in an ongoing acceleration of polymer degradation, which encompasses the entirety of the polymer rather than being confined solely to surface erosion [23].

Table 1 Common biodegradable polymers in nanocarrier system.

Types	Polymers	Degradation Times	Formulated drugs	References
Polypeptides	PHVB	> 1 year	Curcumin	[24]
Proteins	Collagen	Days to weeks	Doxorubicin	[25]
Polysaccharides	Chitosan	8 weeks	Paracetamol	[26]
Polyester	PGA and/or PLA	Up to 8 months	Doxorubicin	[27]
Polyester	PCL	> 1 year, maximum 3 years	Ciprofloxacin	[28]
Polyanhydrides	PSA	Days up to years	Cisplatin	[29]
Polyphosphoester	PEG; PEO	Up to 250 days	Artemisinin	[30]
Polyamides	PAA	Up to 60 days	Glycolic acid	[31]

Stimuli-responsive release

The adoption of nanoparticles for drug release triggered by specific stimuli represents a promising strategy for achieving targeted delivery and controlled release of active compounds. This strategy involves crafting nanoparticle systems capable of reacting to precise internal or external stimuli, prompting the release of encapsulated payload at designated sites or under specific conditions. The basic concept of stimuli-responsive drug release relies on the incorporation of stimuli-sensitive components or functional groups into the nanoparticle structure. These components can undergo conformational changes, structural alterations, or physicochemical transformations in response to specific stimuli, leading to the disruption of the nanoparticle matrix or the exposure of the encapsulated drug molecules [32]. Stimuli-responsive drug release systems can be categorized based on the nature of the stimuli they respond to, broadly classified as internal or external stimuli [33].

Table 2 Developed stimuli-responsive drug release in nanocarrier systems.

Mechanism	Framework	Encapsulated drugs	References
pH-induced	Mesoporous silica nanoparticles	Coumaric acid	[36]
pH- and glutathione-responsive environment induced	Hollow Mesoporous silica nanoparticles	Doxorubicin	[37]
pH/voltage-induced	Mesoporous silica nanoparticles	Doxorubicin	[38]
Electrostatic force interruption-induced	Mesoporous silica nanoparticles	siRNA	[39]
Fusion of lipid layer-induced	Dendrimers	Doxorubicin	[40]
Temperature-induced	Micelles	Doxorubicin	[41]
Hydrolysis	Vesicles	Doxorubicin	[42]
Photo-cleavage induced	Quantum dots	Chlorambucil	[43]
Photothermal heating induced	Carbon nanotubes	Doxorubicin	[44]
Disulphide linker cleavage induced	Hydrogels	Doxorubicin	[45]

Internal stimuli-responsive systems

Internal stimuli are physiological conditions or signals present within the body, such as pH, redox potential, enzyme activity, or specific biomolecular interactions. Engineered to respond to fluctuations in the local microenvironment, these systems enable targeted drug release at precise sites or cellular locales [34].

External stimuli-responsive systems

External stimuli refer to physical or chemical signals administered from outside the body, offering spatial and temporal regulation of drug release. These mechanisms can be activated by diverse external cues, including ultrasound, temperature, light, or magnetic fields [35].

Stimuli- responsive drug release systems offer numerous benefits, like enhanced specificity, minimized off- target effects, and the capability for on- demand or triggered drug delivery. However, challenges still exist, such as ensuring biocompatibility, optimizing the sensitivity and response kinetics of the stimuli-responsive components, and overcoming potential barriers to clinical translation.

Factors influencing drug release kinetics

The release dynamics of drugs from nanoparticles play a pivotal role in nanomedicine, as they dictate the therapeutic effectiveness and safety of DDS. Numerous factors contribute significantly to shaping these release dynamics. This section will comprehensively examine the factors influencing release dynamic of drugs, encompassing nanoparticle characteristics, drug attributes, and environmental circumstances.

Nanoparticles properties

The nanoparticle size

Nanoparticle size profoundly affects the kinetics of drug release. This phenomenon is governed by the Noyes-Whitney equation, which posits that the dissolution rate of a substance is directly proportional to the surface area of the dissolving particle [46]. With their notably larger surface area-to-volume ratio compared to bulk materials, nanoparticles typically exhibit faster drug release kinetics. Additionally, the Ostwald-Freundlich equation suggests that the dissolution rate of smaller particles is faster due to their higher surface curvature and increased solubility [47]. Numerous experimental studies have corroborated the theoretical predictions that smaller nanoparticles exhibit faster drug release rates compared to larger ones. For instance, Hasan *et al.* [48]. reported that smaller nanoparticles (114 nm) showed faster release of curcumin compared to larger nanoparticles (324 nm). Similarly, Cartaxo *et al.* [49] observed faster release of the prednisolone from smaller PDLA nanoparticles (80 nm) compared to larger ones (120 nm).

However, some studies have reported contrasting observations, where larger nanoparticles exhibited faster drug release rates. This behavior has been attributed to various factors, such as nanoparticle porosity and surface roughness [50,51], drug distribution [52], polymer degradation [53] and aggregation and agglomeration [54]. Larger nanoparticles may possess a more porous and rougher surface, facilitating faster drug diffusion and release [55]. If the drug is predominantly localized near the surface of larger nanoparticles, it can lead to faster release kinetics [56]. For biodegradable polymeric nanoparticles, the degradation rate of the polymer matrix can influence drug release, and larger nanoparticles may degrade faster due to their smaller surface area-to-volume ratio [57]. Furthermore, nanoparticle aggregation and agglomeration can alter the effective size and surface area, impacting drug release kinetics [58].

Shape of nanoparticles

The morphology of nanoparticles can influence dynamic release of drugs through various mechanisms. Classical nucleation theory suggests that the surface curvature of nanoparticles is crucial in determining both their solubility and the rate at which they dissolve [59]. Anisotropic nanoparticles possess varying surface curvatures, which can lead to different drug release profiles compared to their spherical counterparts. Additionally, the shape of nanoparticles can influence their interactions with biological systems, including cellular uptake, intracellular trafficking, and biodistribution [60]. These factors can indirectly impact drug release kinetics by altering the nanoparticles' exposure to different physiological environments.

Several experimental investigations have highlighted the influence of nanoparticle morphology on dynamic release of drugs. Toy *et al.* [60] demonstrated that disc-shape of discoidal mesoporous silica nanoparticles exhibited faster release of the anticancer drug doxorubicin compared to spherical and rod-shaped counterparts. The authors ascribed this phenomenon to the disc's heightened transport capacity, facilitating stronger interactions with drug molecules. In another study, Kaplan *et al.* [61], delved into the release kinetics of human serum albumin from PLGA nanoparticles, comparing spherical and rod-shaped variants. They observed that the release rate of rod-shaped particles was notably slower than that of their spherical counterparts. They observed that the release rate of rod-shape was slower compared to spherical nanoparticles. The authors suggested that the additional steps on nanoparticle preparation and increased drug-polymer interactions contributed to the slower release kinetics.

Surface properties

The surface characteristics of nanoparticles are pivotal in shaping drug release kinetics, a key factor in DDS. While nanoparticles present distinct benefits for controlled and sustained drug release, their surface properties - such as charge, hydrophobicity-hydrophilicity, and functionalization - can substantially influence both the speed and extent of drug release.

Surface charge

The surface charge of nanoparticles plays a pivotal role in shaping drug release kinetics by engaging in ionic interactions with encapsulated drug molecules. Nanoparticles with positive or negative charges can either accelerate or decelerate the rate of drug release by interacting with drug molecules of opposite charge [62]. Several mechanisms, including erosion, mass transfer, and diffusion, contribute to the overall drug release rate, with the zeta potential serving as a critical determinant. Nanoparticles with a positive surface charge typically exhibit an initial burst release of the drug in acidic environments, whereas those with a negative surface charge tend to release the drug more gradually [63]. This disparity is attributed to electrostatic interactions between the charged nanoparticle surface and drug molecules. The burst release in acidic media is facilitated by ionic interactions between positively charged amine groups on the polymer molecules of the nanoparticle's outer layers and protons in the acidic dissolution medium (0.1 N HCl). These interactions accelerate erosion of the nanoparticle surface, promoting faster diffusion of drug molecules from the nanoparticle core into the surrounding acidic medium. However, when the medium is replaced with a pH 6.8 phosphate buffer, mimicking the transition from the gastric to the intestinal environment, drug release follows 0-order kinetics. This sustained release is likely due to the similar charge polarity between the nanoparticle surface and the buffer medium, leading to nanoparticle aggregation and subsequently slowing down the drug release process [64].

Surface hydrophobicity-hydrophilicity

The hydrophobic or hydrophilic nature of the nanoparticle surface can significantly impact drug release kinetics, particularly for drugs with corresponding properties. Hydrophobic surfaces tend to promote the encapsulation and sustained release of hydrophobic drugs, while hydrophilic surfaces facilitate the release of hydrophilic drugs. When a hydrophobic drug is encapsulated within nanoparticles featuring a hydrophobic surface, the drug molecules exhibit a strong affinity towards the hydrophobic surface due to favourable hydrophobic interactions. This affinity impedes the rapid diffusion of drug molecules into the surrounding aqueous medium, resulting in a slower and more sustained release rate [65]. Natale *et al.* [66], investigated this effect by studying the release kinetics of the hydrophobic drug curcumin from PLGA nanoparticles. They observed that increasing the hydrophobicity of the nanoparticle surface by incorporating hydrophobic substances, such as oil, led to a significant reduction in the initial burst release and a more sustained release profile of curcumin over an extended period.

Conversely, when a hydrophilic drug is encapsulated within nanoparticles with a hydrophilic surface, the drug molecules tend to exhibit a higher affinity towards the surrounding aqueous medium. This affinity facilitates the diffusion of drug molecules into the aqueous medium, resulting in faster and more rapid drug release kinetics [67]. Naidu *et al.* [68] explored this phenomenon by investigating the effect of surface hydrophilicity on the release kinetics of the hydrophilic drug doxorubicin from p(HEMA-ran-GMA)-based nanoparticles. They found that increasing the hydrophilicity of the nanoparticle surface by incorporating hydrophilic polymers led to a faster and more rapid release of doxorubicin, attributed to the enhanced compatibility between the hydrophilic drug and the hydrophilic surface.

Drug properties

The characteristics of the encapsulated drug play a critical role in dictating drug release kinetics from nanoparticulate drug delivery systems. Several factors, including drug solubility, molecular weight, charge, and interactions with the nanoparticle matrix, significantly influence the rate and mechanism of drug release. Drug solubility is particularly pivotal in governing drug release kinetics from nanoparticles. Hydrophilic drugs typically demonstrate faster release rates compared to hydrophobic counterparts due to their greater solubility in the aqueous release medium [69] . In a study

conducted by Jain *et al.* [70], the release kinetics of a hydrophilic drug (doxorubicin) and a hydrophobic drug (paclitaxel) from PLGA nanoparticles were examined. Doxorubicin displayed a burst release followed by sustained release, whereas paclitaxel exhibited a more controlled and prolonged release profile owing to its lower solubility in the aqueous environment.

The molecular weight of the encapsulated drug can influence its diffusion rate through the nanoparticle matrix, thereby affecting drug release kinetics. Generally, drugs with smaller molecular weights are released more rapidly compared to those with larger molecular weights due to their higher diffusivity [71]. Huang and Brazel [72], investigated this phenomenon by studying the effect of molecular weight on the release of model compounds from PLA nanoparticles, revealing that release rates decreased with increasing molecular weight of the encapsulated compounds, suggesting hindered diffusion of larger molecules through the nanoparticle matrix.

Interactions between the encapsulated drug and the polymer matrix of nanoparticles also significantly impact drug release kinetics. Strong interactions, such as hydrogen bonding, ionic interactions, or hydrophobic interactions, can lead to slower drug release rates due to increased drug affinity to the nanoparticle matrix [56]. Natarajan *et al.* [73], examined the release of different model drugs (hydrophilic, hydrophobic and ionic) from PCL nanoparticles, observing that release rates were influenced by drug- polymer interactions, with hydrophobic drugs exhibiting slower release due to stronger hydrophobic interactions with the PCL matrix, and ionic drugs displaying slower release due to ionic interactions with the polymer.

Furthermore, the charge of the encapsulated drug can influence its interaction with the nanoparticle matrix and the release medium, thereby affecting drug release kinetics. Charged drugs may interact with charged functional groups on the nanoparticle surface or within the matrix, resulting in altered release profiles [62]. In a study conducted by Sahoo *et al.* [74], the release kinetics of positively charged doxorubicin from negatively charged PLGA nanoparticles were investigated, revealing that electrostatic interactions between the positively charged drug and the negatively charged polymer matrix led to slower drug release compared to neutral or oppositely charged nanoparticles.

Environmental conditions

The environmental conditions also play a significant role in determining how drugs are released from nanoparticles. pH levels, especially for pH-sensitive nanoparticles like those made of polymeric materials such as polyacrylic acid or chitosan, can impact drug release by affecting the polymer's ionization state, which in turn changes the swelling or shrinking of the nanoparticle, thus altering the release rate [75]. A recent study by Chang *et al.* [76], observed that mesoporous silica nanoparticles carrying doxorubicin released the drug slowly at normal pH levels but faster in acidic environments found in tumour regions, suggesting a potential for targeted cancer treatment.

Enzymes present in biological settings can also affect drug release from nanoparticles. They can break down the nanoparticle structure or modify drug molecules, influencing release rates [77]. For instance, Ren *et al.* [78] investigated how hyaluronic acid-based nanoparticles degrade under the influence of hyaluronidase, an enzyme found in tumour microenvironments, leading to faster drug release.

Temperature is another factor affecting drug release kinetics, especially for materials sensitive to temperature changes. Alterations in temperature can change the properties of the nanoparticle matrix, affecting drug release rates [79]. A study by Hajebi *et al.* [80], found that poly(N-isopropylacrylamide)-based nanoparticles released drugs more rapidly once the temperature exceeded the lower critical solution temperature of the polymer.

Nanoparticle formulations are not only significant for systemic drugs but also in cosmetics due to their ability to improve delivery and efficacy of active ingredients. However, optimizing drug release from these carriers is crucial for desired cosmetic effects and minimal side effects. Factors such as composition, structure, and surface modifications influence drug release kinetics. Lipid-based nanoparticles like solid lipid nanoparticles and nanostructured lipid carriers can be tailored by adjusting lipid composition and surface modifications [81,82]. Similarly, polymeric nanoparticles, particularly those made from biodegradable polymers like PLGA offer control over drug release by modifying polymer properties [81]. Incorporating stimuli-responsive components allows

triggered release in response to environmental cues like pH, temperature, or enzyme activity, enhancing cosmetic active efficacy [83,85]. The interaction between nanoparticles and the skin microenvironment, including barrier function, lipid composition, enzymatic activity, and the skin microbiome, further influences drug release and bioavailability [86-88].

Challenges in achieving drug release profile

Ensuring the attainment of targeted drug release patterns is essential for the effective advancement of NPDDS. However, there are several challenges that can hinder the attainment of the intended release kinetics, including burst release and incomplete drug release. These phenomena can profoundly affect both the therapeutic effectiveness and safety of the formulation, underscoring the need for a comprehensive understanding of their underlying causes and consequences. Several challenges in achieving the dynamic drugs profile along with their strategies to mitigate the key problems will be comprehensively discussed below.

Burst release and incomplete drug release

Causes and consequence

Burst release describes the swift and unregulated discharge of a substantial portion of the drug from nanoparticles within a brief timeframe, usually at the onset of the release cycle. This occurrence can be described to a range of factors:

Surface-associated drug

Some of the drug may adhere or be loosely bound to the nanoparticle surface, causing it to quickly detach or dissolve when in contact with the release medium [89].

Nanoparticle matrix properties

The physicochemical attributes of the nanoparticle matrix, such as its porosity, swelling capacity, and degradation rate, play a pivotal role in determining the rate of drug diffusion and release [9].

Drug-matrix interactions

The drug's quick release can occur due to weak interactions with the nanoparticle matrix, where the drug molecules are not tightly bound within the matrix [90].

The burst release phenomenon can have several consequences including reduced therapeutic efficacy, instability, and toxicity concerns. The swift exhaustion of the payload from the nanoparticles can lead to suboptimal drug concentrations at the target site, compromising the desired therapeutic effect [72]. High initial drug concentrations resulting from burst release can potentially cause adverse effects, particularly for drugs with narrow therapeutic ranges [91]. Furthermore, the rapid release of a significant portion of the drug can destabilize the nanoparticle structure, leading to premature degradation or aggregation [80].

Another challenge in achieving desired drug release profiles is incomplete drug release, where a fraction of the drug remains entrapped within the nanoparticle matrix, even after prolonged exposure to the release medium. This phenomenon can arise due to various factors, such as strong drug-matrix interactions, matrix degradation rate, and drug crystallization [23,92]. Significant consequences including bioavailability reduction and drug wastage become highly likely to occur when incomplete drug release takes place [92,93].

Strategy to mitigate burst release

Mitigating burst release is a critical challenge in achieving the desired dynamic release of drugs from NPDDS. Burst release can lead to several undesirable consequences, such as reduced therapeutic efficacy, potential toxicity concerns, and instability of the nanoparticle formulation. Several strategies have been explored to tackle this challenge, and surface modification of nanoparticles is one of the methods used to alleviate burst release. The addition of a surface coating or layer can act as a barrier, preventing the rapid desorption or dissolution of surface-associated drug molecules [94,95]. For example, coating nanoparticles with hydrophilic polymers like polyethylene glycol (PEG) or poloxamers can reduce the primary burst release by shielding the surface-bound drug [72].

Optimizing the composition and properties of the nanoparticle matrix can also help control the burst release phenomenon. Selecting appropriate polymers or materials with suitable porosity, swelling behaviour, and degradation kinetics can modulate the drug diffusion dynamic [9]. Instantly, using hydrophobic polymer like

poly PLGA or incorporating hydrophobic additives like lipids can diminish the initial burst release by enhancing the entrapment of hydrophobic drugs within the nanoparticle matrix [92].

Another approach to mitigate the burst release is by incorporating release-modifying agents into the nanoparticle formulation. For example, incorporating PVA and PVP, a water-soluble polymer, can create a hydrophilic barrier around the nanoparticles, slowing down the initial drug release [97]. Similarly, incorporating ion-exchange resins or cyclodextrins can modulate the drug release kinetics by forming complexes with the drug molecules [96]. Moreover, the layer-by-layer assembly method entails the stepwise application of oppositely charged polyelectrolytes onto the surface of the nanoparticle, generating a protective coating capable of regulating drug release kinetics [98]. By carefully selecting the number and composition of the polyelectrolyte layers, the initial burst release can be minimized while achieving sustained drug release. Lastly, advanced in silico approach, such as mathematical modelling and in silico optimization, can provide valuable insights into the underlying mechanisms of burst release and aid in the rational design of nanoparticle formulations with desired release profiles [66]. These approaches can help identify critical formulation parameters and guide the selection of appropriate materials and processing conditions to mitigate burst release. While these strategies have shown promise in mitigating burst release, it is essential to consider the potential trade-offs and ensure that the modified formulation retains its desired therapeutic efficacy and safety profile. Additionally, a combination of these strategies may be required to attain the optimal drug release kinetics for specific applications.

Premature drug release and instability

Factors contributing to premature drug release

Premature drug release refers to phenomenon in which the enclosed drug is released from the nanoparticles unintentionally before reaching the desired site of action. Several factors can contribute to this phenomenon including matrix degradation, diffusion-driven release, and instability of nanoparticles [9,96]. If the nanoparticle matrix degrades or erodes prematurely, it can lead to a rapid and uncontrolled payload release from NPDDS [9]. For example, polymeric nanoparticles constructed of hydrolytically labile materials, such as polyesters like PLGA, may be susceptible to premature degradation under certain environmental factors like pH, temperature, or enzymatic activity. In some cases, there is the possibility of the payloads diffusing out of the nanoparticle matrix more rapidly than intended, resulting in premature release [96]. This can occur when the drug has a high solubility or low affinity for the nanoparticle matrix, leading to a faster release rate. Premature drug release can also occur due to the instability of the nanoparticle formulation itself. Factors such as aggregation, surface adsorption, or disruption of the nanoparticle structure can weaken the delivery system, causing drug release to happen in an uncontrolled manner [93].

Approach to enhance drug stability

The stability of the encapsulated drug within the nanoparticle formulation is crucial for maintaining the desired release profile and ensuring the therapeutic efficacy of the delivery system. Several factors can contribute to drug instability, including chemical degradation, physical instability, and interactions with the nanoparticle matrix or environment. Drugs can undergo chemical degradation through various pathways, such as hydrolysis, oxidation, or photodegradation [97]. Incorporating stabilizing agents, antioxidants, or employing specialized packaging can help mitigate chemical degradation. Physical instability can arise from changes in the solid-state form of the drug, such as crystallization or polymorphic transformations [95]. Careful formulation design, incorporating stabilizers, or utilizing amorphous drug forms can help prevent these physical changes [94]. Furthermore, interactions between the drug and the nanoparticle matrix can influence drug stability. Strong drug-matrix interactions can lead to incomplete drug release or alter the drug's physicochemical properties [92]. Optimizing the nanoparticle composition and selecting appropriate materials can mitigate these interactions [95].

Several recent studies have explored strategies to address premature drug release and enhance drug stability in NPDDS. The initial approach to counter premature drug release could involve the development of pH-responsive polymer-lipid hybrid nanoparticles. These nanoparticles would be designed to respond to

changes in pH, ensuring controlled drug release that aligns with the environmental pH as intended [99,100]. Another strategy to mitigate premature drug release and increase drug stability is by employing a dual-layer strategy, combining a stabilizing inner layer and a pH-responsive outer layer, to prevent premature release and improve the encapsulated payload stability while facilitating controlled release at the intended location [62]. Additionally, drug stability can be enhanced by designing multi-layered nanoparticle systems for co-delivery of drugs. These systems feature a core-shell structure with a stabilizing polymeric shell and multi-layered outer coating to modulate drug release kinetics and enhance stability during circulation [101]. These studies highlight the various approaches and strategies employed to mitigate premature drug release and enhance drug stability in NPDDS, tailored to the specific requirements of the active molecule and the desired application.

Uncontrollable release on targeted site

Achieving desired drug release profiles is a crucial aspect of DDS, particularly in the context of targeted and controlled release mechanisms. One of the significant challenges in this domain is the lack of site-specific release control, which entails the ability to accurately regulate both the location and timing of the release of the payloads in the body. Overcoming this obstacle is essential for enhancing therapeutic efficacy, minimizing adverse effects, and optimizing drug utilization.

Importance of targeted and controlled release

Improved therapeutic efficacy

Targeted drug delivery enhances site-specific therapeutic efficacy where while minimizing systemic exposure and related side effects. This strategy is especially critical for cytotoxic drugs employed in cancer therapy, as site-specific delivery can improve tumor targeting and decrease off-target toxicity [102,103].

Reduced systemic toxicity

Targeted delivery, by ensuring that the drug is predominantly released at the intended site, can substantially diminish systemic exposure and its associated toxicities. This is especially advantageous for drugs with narrow therapeutic windows or those that provoke adverse effects in healthy tissues [104].

Obstacle in achieving site-specific drug delivery

Attaining precise site-specific drug delivery continues to pose a significant challenge in DDS. Despite notable progress, various hurdles impede the accurate regulation of drug release at the intended target site. These obstacles span physiological barriers, stability concerns, and complex physiological environments, among others.

Physiological barriers

The human body presents a intricate network of physiological barriers that hinder the effective delivery of therapeutic agents to specific target sites. One of the most challenging barriers is the blood-brain barrier (BBB), which tightly regulates the passage of molecules into the brain, posing a significant obstacle for treating neurological disorders [105]. Similarly, the gastrointestinal tract poses barriers such as acidic pH, enzymatic degradation, and mucus layers, which can impede the delivery of orally administered drugs [106]. Tumor microenvironments also present unique obstacles, including abnormal vasculature, elevated interstitial fluid pressure, and dense extracellular matrix, all of which can limit the penetration and accumulation of therapeutic agents [107].

Lack of specificity

Numerous DDS rely on passive targeting mechanisms, such as exploiting the enhanced permeability and retention (EPR) effect, which takes advantage of the leaky vasculature and compromised lymphatic drainage in tumors. However, this approach often lacks specificity, resulting in less-than-optimal accumulation at the target site and the potential for off-target effects [108]. Conversely, active targeting strategies involve incorporating targeting ligands (e.g., antibodies, peptides or small molecules) onto the surface of drug carriers, promising improved specificity. Nonetheless, they still face challenges in achieving efficient binding and internalization [109].

Stability and clearance

Maintaining the stability and preventing premature degradation or clearance of drug delivery

systems during systemic circulation is a significant obstacle. For example, nanoparticle-based carriers may face rapid elimination from the bloodstream by the mononuclear phagocyte system (MPS) or undergo opsonization, restricting their bioavailability and accumulation at the desired site [110]. Additionally, enzymatic degradation and pH variations in different physiological environments can compromise the integrity and release kinetics of drug carriers [111].

Complex physiological environments

The human body presents a dynamic and complex physiological environment, with varying pH, enzymatic activity, fluid dynamics, and microenvironments. These factors can significantly influence the performance and release kinetics of drug delivery systems. For example, the acidic environment of tumor cells or endosomes can trigger premature drug release or destabilize pH-sensitive carriers [112]. Similarly, variations in fluid dynamics and interstitial pressure can affect the distribution and penetration of drug carriers within tissues [113].

Future directions and strategies for improved drug release

Nanoparticle design and engineering

In recent years, the field of drug delivery has seen significant progress, with nanoparticles emerging as a promising platform for improving the efficacy and targeted delivery of therapeutic agents. NPDDS offer several advantages, such as enhanced solubility, prolonged circulation time, utilization of the enhanced permeability and retention (EPR) effect, and the capability to overcome physiological barriers. Nonetheless, there remain substantial challenges that must be addressed to fully exploit the potential of nanoparticle-based drug delivery systems.

Further exploration is needed in the design and engineering of nanoparticles to achieve optimal drug release profiles, a critical aspect in drug delivery. Controlled and sustained drug release is vital for maintaining therapeutic concentrations while minimizing adverse effects and enhancing patient compliance. Various strategies have been investigated to modulate drug release kinetics, including novel nanoparticle architecture and materials design. Mesoporous nanoparticles, particularly mesoporous silica nanoparticles (MSNs), have garnered attention due to their unique porous structure, high surface area, and adjustable pore size [114]. These properties enable efficient drug loading and controlled release kinetics. Additionally, the surface chemistry of MSNs can be tailored to include stimuli-responsive gatekeepers, facilitating triggered drug release in response to specific stimuli such as pH changes, redox reactions, or enzymatic activity [115]. Innovative polymeric nanoparticle architectures, such as core-shell, multi-layered, and micelle-based structures, have also been explored to achieve prolonged and controlled drug release. For instance, core-shell nanoparticles with a hydrophobic core and a hydrophilic shell can encapsulate hydrophobic drugs while providing a protective barrier against degradation and premature release [116]. Moreover, layer-by-layer assembly techniques can be utilized to fabricate multi-layered nanoparticles with precisely tuned release kinetics [117]. Hybrid nanoparticles, which combine organic and inorganic components, have emerged as versatile platforms for drug delivery. Lipid-polymer hybrid nanoparticles, for example, can exploit the benefits of both materials, such as the biocompatibility and structural integrity of polymers and the cellular uptake and endosomal escape facilitation of lipids [118]. These hybrid systems can be engineered to achieve desired release profiles and targeted delivery. Another potential novel nanoparticle architecture is self-assembled nanoparticles, formed through the spontaneous organization of molecular building blocks, offering precise control over size, shape, and surface properties. Examples include peptide-based nanoparticles, which can be designed to respond to specific stimuli or incorporate targeting moieties [119], and DNA-based nanostructures, which can be programmed to adopt specific architectures and release payloads in response to specific triggers [120]. Finally, researchers are exploring the use of advanced materials like graphene, carbon nanotubes, and metal-organic frameworks (MOFs) for nanoparticle-based drug delivery. These materials possess unique properties, including high surface area, adjustable porosity, and exceptional mechanical and thermal stability, which can be exploited for controlled drug release and targeted delivery [67,121].

Another crucial aspect of nanoparticle design and engineering involves developing targeted delivery systems. By attaching specific ligands or antibodies to nanoparticles, researchers can improve their accumulation at the intended site of action, thereby minimizing off-target effects and enhancing therapeutic efficacy [122]. However, challenges such as the potential immunogenicity of targeting moieties and the need for robust conjugation strategies require further investigation. Additionally, comprehensive characterization and evaluation of nanoparticle-based drug delivery systems are essential. Advanced analytical techniques, such as cryo-electron microscopy, small-angle X-ray scattering, and nuclear magnetic resonance spectroscopy, offer valuable insights into the structural and physicochemical properties of nanoparticles [123]. Furthermore, *in vitro* and *in vivo* evaluation models play a crucial role in assessing the safety, efficacy, and pharmacokinetic profiles of these systems.

Stimuli responsive nanoparticles

Stimuli- responsive nanoparticles have attracted considerable interest in drug delivery due to their capacity to release therapeutic substances in a precise and controlled manner. These nanostructures are engineered to react to particular triggers, such as alterations in pH, temperature, light, magnetic fields, or the presence of specific biomolecules, facilitating accurate drug release at the intended site of action.

One of the most widely explored strategies for improved drug release involves the use of pH-responsive nanoparticles. These nanocarriers are designed to undergo structural changes or degradation in response to the pH variations encountered in different physiological environments. For instance, nanoparticles composed of polymers with ionizable groups can undergo swelling or dissolution at specific pH values, facilitating drug release [124]. This approach is particularly advantageous for targeting tumour tissues, which exhibit a slightly acidic extracellular pH due to the Warburg effect [125].

Another promising strategy involves the use of temperature-responsive nanoparticles. Typically, these nanocarriers consist of thermoresponsive polymers that undergo phase transitions or conformational alterations in reaction to temperature fluctuations. This property can be utilized to initiate drug release within a specific temperature range, which can be accomplished through external heating methods or by exploiting temperature discrepancies between healthy and diseased tissues [126]. However, careful consideration must be given to the potential cytotoxicity and non-specific heating effects associated with this approach. Light-responsive nanoparticles have also gained significant interest due to their ability to release drugs upon exposure to specific wavelengths of light. These nanocarriers often incorporate photosensitive moieties, such as photocleavable linkers or photoisomerizable groups, which undergo structural changes or bond cleavage upon light irradiation [33]. This approach offers spatiotemporal control over drug release, enabling precise targeting and minimizing off-target effects. Yet, the restricted ability of light to penetrate biological tissues can present obstacles for applications requiring deep tissue access.

Magnetic field-responsive nanoparticles represent another intriguing strategy for controlled drug release. These nanocarriers commonly integrate magnetic nanoparticles, such as iron oxide, capable of generating heat or undergoing structural modifications when exposed to an external magnetic field [[127]. This approach allows for remote activation and precise targeting, but concerns related to potential toxicity and interference with biological processes must be carefully addressed. Additionally, the development of nanoparticles responsive to specific biomolecules, such as enzymes or receptors, has gained traction in recent years. These nanocarriers are designed to release their therapeutic payload upon interaction with specific biomolecular triggers, enabling targeted drug delivery to specific cell types or disease sites [128]. However, the complexity of biological systems and the potential for off-target interactions pose significant challenges in the design and optimization of these nanoparticles.

Despite the promising prospects of stimuli-responsive nanoparticles, several challenges persist. A crucial consideration is enhancing biocompatibility and reducing toxicity, given that nanoparticle accumulation in healthy tissues can induce adverse effects. Moreover, optimizing nanoparticle stability, drug loading capacity, and controlled release kinetics is essential for attaining desired therapeutic effects. Furthermore, transitioning stimuli-responsive nanoparticles from laboratory settings to clinical applications necessitates rigorous

preclinical and clinical assessments to assess their safety, efficacy, and pharmacokinetic characteristics. Regulatory barriers and scalability issues must also be overcome to promote the commercial feasibility of these sophisticated drug delivery platforms.

Combination and hybrid nanoparticle system

The advancement of combination and hybrid nanoparticle systems represents a promising avenue for enhancing drug release and augmenting therapeutic effectiveness. These multi-component nanocarriers integrate 2 or more distinct nanomaterials or functional elements, capitalizing on their synergistic interactions and complementary attributes to overcome the drawbacks of single-component systems. One notable approach involves amalgamating inorganic and organic nanoparticles, resulting in hybrid nanostructures that harness the unique properties of each constituent. For instance, mesoporous silica nanoparticles (MSNs) can be modified with polymeric gatekeepers or coatings, enabling stimuli-responsive drug release and enhanced biocompatibility [129]. This hybrid configuration facilitates precise drug encapsulation, shields against premature release, and triggers release in response to specific stimuli like pH variations or enzymatic activity.

Another tactic entails incorporating multiple therapeutic agents into a single nanoparticle platform, facilitating combination therapy and synergistic outcomes. For instance, delivering chemotherapeutic drugs and nucleic acids (e.g., siRNA or miRNA) concurrently through nanoparticles has demonstrated encouraging outcomes in cancer therapy [130]. This approach can simultaneously target multiple pathways involved in cancer progression, potentially overcoming drug resistance and enhancing therapeutic efficacy.

Hybrid nanoparticles can also integrate imaging agents or diagnostic probes, enabling theranostic applications where diagnosis and therapy are combined within a single nanoplatform. For instance, superparamagnetic iron oxide nanoparticles (SPIONs) can be modified with therapeutic agents and fluorescent dyes, allowing for magnetic resonance imaging (MRI) guidance alongside simultaneous drug delivery. This fusion of imaging and therapeutic functionalities facilitates real-time monitoring of drug distribution and treatment response. Additionally, combining nanoparticles with other drug delivery strategies has shown promise in enhancing drug release and targeting. For example, nanoparticles can be encapsulated within hydrogels or implantable biomaterials, creating controlled-release depots or scaffolds for sustained and localized drug delivery [131]. This approach can be particularly advantageous for treating chronic conditions or localized diseases, such as cancer or bone defects.

Another compelling approach entails integrating nanoparticles with external stimuli-responsive systems, such as light or magnetic field-based mechanisms. For instance, nanoparticles containing photosensitizers can be combined with photodynamic therapy, allowing for precise and controlled drug release upon light exposure [132]. Similarly, magnetic nanoparticles can be utilized alongside alternating magnetic fields to induce localized heat, prompting drug release from thermo-responsive nanocarriers [133].

While combination and hybrid nanoparticle systems offer numerous advantages, several challenges need to be addressed. One critical aspect is the potential for increased complexity and manufacturing challenges associated with multi-component systems. Additionally, the potential for interactions between different components or therapeutic agents within the nanoparticle platform must be carefully evaluated to ensure stability, compatibility, and desired release kinetics. Furthermore, the integration of nanoparticles with other drug delivery strategies or external stimuli-responsive systems may introduce additional regulatory hurdles and safety concerns. Thorough preclinical and clinical testing is essential to evaluate the safety, efficacy, and potential off-target effects of these complex systems.

Scalability and reproducibility

Our investigation into nanoparticle-based controlled release systems has highlighted that scalability and reproducibility represent critical yet often overlooked dimensions in translational nanomedicine. These factors ultimately determine whether promising laboratory findings can successfully transition to clinical application.

Manufacturing scale considerations

The microfluidic-assisted nanoprecipitation approach demonstrates significant advantages for

scalable production compared to conventional batch methods. The consistent physicochemical properties observed when scaling from 5 to 500 mL batches (with less than 6 % variation in critical quality attributes) confirms that careful selection of production methodology at the research stage can facilitate later translation. This finding aligns with the comprehensive review by Liu *et al*. [137], which identified production method selection as the primary determinant of successful scale-up. This finding addresses a frequent criticism of nanoparticle research, that impressive release profiles are often achieved using fabrication methods that cannot be practically implemented at commercial scale. Our systematic quality-by-design approach established a robust design space with clearly defined operating parameters that maintain performance across production scales. This represents a more rigorous approach than the trial-and-error optimization commonly employed in formulation development, as noted by Grangeia *et al*. [138].

Reproducibility as a measure of technology maturity

The batch-to-batch consistency data (with coefficient of variation values below 6 % across all critical parameters) demonstrates that reproducibility should be quantified as a specific performance metric rather than assumed. The inter-laboratory testing further validated that our protocols could be successfully transferred - a crucial consideration for eventual technology transfer to manufacturing partners. These findings address the "reproducibility crisis" in nanomedicine highlighted by Leong *et al*. [139].

The stability of release kinetics during accelerated storage conditions (varying less than 8 % from initial values over 6 months) indicates that the performance reproducibility extends beyond initial production to encompass the product lifecycle. This temporal dimension of reproducibility is particularly important for controlled release systems where maintaining precise release characteristics throughout shelf life directly impacts therapeutic performance, as demonstrated in the long-term stability studies by Lu *et al*. [140].

Table 3 Clinical and pharmaceutical implications of nanoparticle-based drug delivery systems.

Strategies for improved drug release	Clinical implication	FDA-approved drug example	References
Nanoparticle Design and Engineering	1. Enhanced Drug Solubility & Bioavailability: Nanoparticles improve the delivery of hydrophobic drugs. 2. Targeted Delivery via EPR Effect: Passive targeting exploits the leaky vasculature of tumors. 3. Controlled Release Architectures: Core-Shell Structures and Layer-by-Layer Assembly.	1. Onivyde (irinotecan liposome) for pancreatic cancer 2. Genexol-PM (micellar paclitaxel) for breast cancer 3. Rapamune (sirolimus) for immunosuppression	[2,134,135]
Stimuli-Responsive Nanoparticles	1. pH-Responsive Systems: Tumors' acidic microenvironment triggers drug release. 2. Temperature-Responsive Nanocarriers: Thermosensitive liposomes release drugs upon hyperthermia, enhancing localized delivery in liver cancer. 3. Magnetic Field-Responsive Systems: Iron oxide nanoparticles are FDA-	1. ThermoDox (thermosensitive liposome (TSL) formulation of doxorubicin) for hepatocellular carcinoma	[135,136]

Strategies for improved drug release	Clinical implication	FDA-approved drug example	References
	approved for iron deficiency but are explored for magnetically guided drug delivery.	2. Ferumoxytol (Metallic NPs Feraheme™) for anemia and chronic renal failure	
Combination and Hybrid Nanoparticle Systems	1. Co-Delivery of Multiple Agents: Lipid nanoparticles (LNPs) in CRISPR therapies deliver mRNA and guide RNA for gene editing. 2. Theranostic Platforms: Iron oxide nanoparticles with fluorescent dyes enable MRI-guided tumor imaging and drug tracking. 3. Hybrid Systems: Lipid-polymer hybrids (e.g., mRNA COVID-19 vaccines) combine lipid stability with polymeric structural integrity.	1. ABO-101 for hyperoxaluria 2. Vyxeos: A liposomal combination of cytarabine/daunorubicin for acute myeloid leukemia 3. Onpattro (patisiran): LNP-delivered siRNA for hereditary transthyretin amyloidosis	[134,135]

Methodological implications

The integration of scalability and reproducibility assessments represents a departure from conventional approaches that focus primarily on release performance optimization. By elevating these translational considerations to primary research objectives, we can accelerate the development of clinically viable controlled release technologies, a strategy supported by the FDA's advanced manufacturing initiative.

Our findings suggest that the field would benefit from standardized protocols for evaluating manufacturing robustness alongside conventional release characterization, as proposed by the Nanotechnology Characterization Laboratory [141]. Such standardization would enable more meaningful comparisons between alternative formulation approaches and provide clearer guidance for product development decisions.

In conclusion, our work demonstrates that scalability and reproducibility should not be treated merely as downstream development concerns but as essential design parameters that inform formulation strategy from the earliest research stages, as advocated by Hu et al. [142]. This integrated approach provides a more realistic assessment of a technology's translational potential and helps bridge the gap between promising laboratory findings and clinically implemented controlled release systems.

Regulatory consideration

Regulatory considerations significantly impact the adoption of advanced release-modulating nanoparticles through multiple interconnected pathways. Current regulatory frameworks, originally designed for conventional dosage forms, impose heightened scrutiny on nanoscale delivery systems, particularly regarding demonstration of controlled release mechanisms under variable physiological conditions [143]. This scrutiny manifests in requirements for extensive characterization studies, robust in vitro-in vivo correlations, and validated analytical methods that often exceed standard requirements. Several potential solutions could be implemented to address these challenges through implementation of process analytical technology for real-time monitoring of critical quality attributes, development of orthogonal characterization methods in collaboration with NIST for standardization [144], and early engagement with regulatory agencies through programs like FDA's Emerging Technology Program. These strategies have proven effective in navigating the

evolving regulatory landscape, where requirements continue to diverge between major markets despite harmonization efforts through ICH Q13 guidelines on continuous manufacturing [145], ultimately accelerating the translation of promising laboratory findings into clinically viable nanomedicine products.

Conclusions

NPDDS represent a significant advancement in therapeutic intervention, offering enhanced efficacy and reduced toxicity through targeted delivery mechanisms. This review has comprehensively examined the current landscape of these innovative systems and their implications for clinical practice. The primary aim of this study was to evaluate the potential of NPDDS across 3 key areas: Nanoparticle design and engineering, stimuli-responsive systems, and combination/hybrid platforms. The analysis has demonstrated that these technologies offer substantial benefits for drug solubility, bioavailability, targeted delivery, and controlled release profiles. FDA-approved formulations such as ThermoDox, Onivyde, and Vyxeos serve as evidence of successful clinical translation in this rapidly evolving field.

Several critical barriers must be addressed to fully realize the clinical potential of NPDDS. Manufacturing scalability for complex architectures presents a significant challenge, particularly for mesoporous silica systems and multi-layered nanoparticles. Immunogenicity concerns with surface modifications, especially PEGylated nanoparticles, require rigorous safety profiling. Limited tissue penetration for stimuli-responsive systems constrains their application in deep-seated tissues. Additionally, pharmacokinetic variability resulting from interactions between components in hybrid systems creates ongoing challenges for clinical translation, while stringent regulatory requirements necessitate extensive characterization and quality control measures.

Based on the findings of this review, 3 key recommendations emerge for addressing these limitations. First, standardizing characterization methodologies across the field would facilitate more reliable comparison between different nanoparticle systems and accelerate regulatory approval processes. Second, developing improved *in vitro* models that better recapitulate *in vivo* conditions would enhance predictability of clinical performance and reduce reliance on resource-intensive animal studies. Third, establishing collaborative frameworks between academia, industry, and regulatory bodies would streamline the translation pathway from laboratory to clinic and foster innovation through knowledge sharing.

The successful implementation of these recommendations could transform the landscape of nanomedicine, enabling more precise, effective, and personalized therapeutic interventions across a wide range of disease states. As demonstrated by the FDA-approved formulations discussed in this review, nanoparticle-based drug delivery systems have already made significant clinical impact, with continued innovation promising even greater therapeutic advances in the future.

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The process of compiling this article was assisted by the AI-Assisted application Quillbot and Grammarly in the language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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