

Stimuli-Responsive Dual Compartment Hybrid Microemulsion Nanoparticle System Enabling Spatiotemporally Controlled Drug Release and Site-Specific Activation

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Received: 28th Feb, 2026; Revised: 6th March 2026; Accepted: 7th April, 2026; Available Online: 20th April, 2026

ABSTRACT

Hydrogel-nanoparticle composite dual-drug delivery systems have become a flexible platform for delivering two different therapeutic agents in a regulated, targeted, and effective manner. This method offers synergistic advantages in a range of biomedical applications by combining the improved stability and targeting capability of nanoparticles with the high loading capacity and adjustable release characteristics of hydrogels. Even though there has been a lot of development, prior studies have mostly concentrated on single-drug systems or straightforward co-delivery techniques, which frequently lack fine spatial and temporal control. The necessity for more complex composite designs that allow for programmable, multi-phase release is highlighted by this gap. Recent developments in hydrogel composition and nanoparticle engineering have made it possible to precisely control medication release and enhance therapeutic results. Hydrogel-nanoparticle composites used in dual-drug delivery systems offer a viable way to get beyond the drawbacks of traditional monotherapy and achieve synergistic therapeutic benefits. The design, effectiveness, and safety of these systems are being improved by ongoing research, opening the door for their clinical application.

Keywords: Stimuli responsive drug delivery, Hybrid microemulsion nanoparticles, Spatiotemporal drug release, Site-specific drug activation

How to cite this article: Pudi P, Savalapurapu L, Pavani M, Sirisha AV, Ketha A, Bhukya JSSN, Bhamidipati SV, Ketha S. Stimuli-Responsive Dual Compartment Hybrid Microemulsion Nanoparticle System Enabling Spatiotemporally Controlled Drug Release and Site-Specific Activation. *Int J Drug Deliv Technol.* 2026;16(46s): 611-616. DOI: 10.25258/ijddt.16.46s.66

Source of support: Nil.4

Conflict of interest: None

INTRODUCTION

Hydrogel-nanoparticle composite dual-drug delivery systems have become a flexible platform for delivering two different therapeutic agents in a regulated, targeted, and effective manner. This method offers synergistic advantages in a range of biomedical applications by combining the improved stability and targeting capability of nanoparticles with the high loading capacity and adjustable release characteristics of hydrogels. Even though there has been a lot of development, prior studies have mostly concentrated on single-drug systems or straightforward co-delivery techniques, which frequently lack fine spatial and temporal control. Because of their

many benefits, nanoparticles have been employed extensively as cancer treatment vehicles. A variety of nanocarriers, including liposomes, polymeric micelles, silica nanoparticles, chitosan nanoparticles, and protein nanoparticles, are being produced¹. Many poorly water-soluble medications can be made soluble by encapsulating them in nanocarriers with amphiphilic characteristics². Moreover, pharmaceuticals can be protected by nano-encapsulation or by endocytosing nanoparticles. The capacity to distinguish cancer cells from healthy cells and remove cancer cells only is a major benefit of employing nanoparticles in chemotherapy^{3,4}. Through an improved permeability and retention effect (EPR), nano-formulated

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medications can evade the body's quick clearance, enabling both passive tumour accumulation and active tumour accumulation by including ligands that target cancer cells⁵. Studies on NFCD are being actively carried out because of these benefits, and some have even advanced to the stage of clinical trials^{6,7}.

Significance of dual drug delivery systems

Although single-drug therapy has demonstrated some efficacy in treating a range of illnesses, the complexity of conditions such as cancer, immunological disorders, and persistent infections frequently limits the therapeutic

efficacy of monotherapy. More sophisticated delivery techniques are needed to address problems such as medication resistance, compensatory signalling pathways, and different pharmacokinetic characteristics. Because dual-drug delivery systems can provide two medicines concurrently or in a controlled sequential manner, they have attracted significant attention in this area⁸. This approach is particularly crucial for diseases with a multi-target pathophysiology, such as solid tumours with various microenvironments or transplant immunology, where co-locating immunosuppressants and anti-inflammatory drugs at the graft site is required⁹.

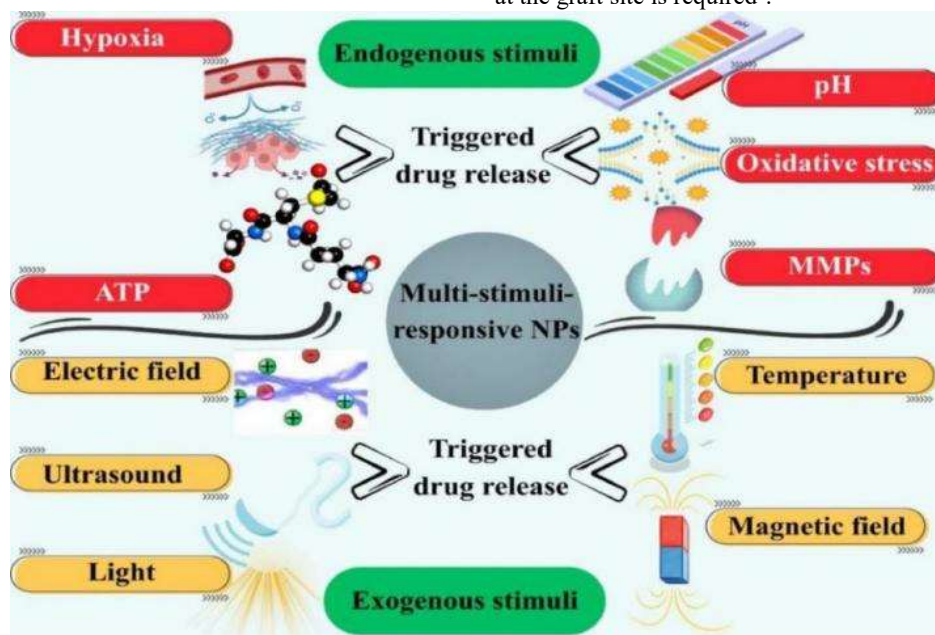


Fig 1: Diagram illustrating a Multi-stimuli-responsive Nanoparticle (NP) system designed for triggered drug release¹⁰

Criteria for hydrogel nanoparticle composites

The exact and independent regulation of each therapeutic agent's release profiles, spatial localisation, and pharmacokinetic behaviours is what gives dual-drug delivery systems their therapeutic benefit, rather than just the co-administration of two therapeutic agents^{11,12}. By combining the adjustable, stimuli-responsive qualities of hydrogels with the compartmentalised loading and controlled release characteristics of nanoparticles, hydrogel–nanoparticle composites have emerged as one of the most promising delivery platforms¹³. High drug loading capacity, surface modification targeting capabilities, and—most importantly—stimuli-responsive behaviour are just a few of the major benefits that nanoparticles provide. Researchers can accomplish site-specific and condition-triggered drug release by designing nanoparticles to react to endogenous cues such as pH changes, reactive oxygen species (ROS), enzyme activity, or temperature gradients^{14,15}.

Design and Fabrication Strategies of Hydrogel–Nanoparticle Dual-Drug Delivery Systems

Physical Embedding

Physical embedding, in which pre-formed nanoparticles are distributed throughout the hydrogel network via non-covalent interactions, is the simplest and most popular method for incorporating nanoparticles into hydrogel matrices¹⁶. This approach is particularly appealing for drug delivery systems that need modular design and quick prototyping because of its operational simplicity, scalability, and minimal chemical alteration of components^{17,18}. The approach does have certain drawbacks, though. The heterogeneous distribution of nanoparticles during gelation, especially in bulk hydrogels, is a significant obstacle that might result in uneven drug release¹⁹.

Covalent Integration

Covalent integration is a crucial design technique for sophisticated hydrogel–nanoparticle composite systems because it enables improved structural stability and precise control over drug release profiles, whereas physical embedding offers simplicity and biocompatibility²⁰. This method creates a strong and functionally cohesive platform that excels in mechanical strength, in vivo retention, and sustained delivery by chemically bonding

nanoparticles to the hydrogel matrix. While the covalently linked nanoparticle domain can react selectively to pH, ROS, enzymatic activity, or other stimuli to initiate the secondary release, the hydrogel matrix can be responsible for the quick or prolonged release of one drug via passive diffusion. For situations requiring staggered pharmacological effects, this architecture enables orthogonal kinetics²¹.

Layer-by-Layer Assembly

Layer-by-layer (LbL) assembly is a bottom-up fabrication technique that alternatively deposits materials layer by layer to produce multilayered structures. This technique has shown itself to be straight forward, economical, and extremely adaptable over the last few decades, allowing for exact control over composition and architecture at the nanoscale scale. By physically separating two therapeutic substances into different layers or domains, LbL assembly provides fine control in the setting of dual-drug delivery. Different medications can be kept apart and protected by this layered architecture²².

Mechanisms of Drug Release in Dual-Drug Delivery Systems

Simultaneous and Sequential Release

The choice between simultaneous and sequential release strategies in dual-drug delivery systems is heavily influenced by therapeutic goals, drug-drug interactions, and the pathological milieu of the target tissue. These

methods impose particular limitations on the material composition and structural design of hydrogel–nanoparticle composites. This strategy allows one agent—often referred to as a priming drug—to shape the microenvironment before the second agent is released²³.

Separation of Space in Composite Structures

Treatments must be spatially isolated inside the carrier structure in dual-drug delivery systems in order to achieve independent release kinetics, site-specific distribution, and low drug-drug interference. By physically dividing the two drugs into separate structural compartments, hydrogel–nanoparticle composites provide multifunctionality within a single delivery system. The double-matrix or core-shell design is a conventional setup where a hydrophilic drug is added to the hydrogel matrix and a hydrophobic drug is enclosed in nanoparticles²⁴.

Drug Release in Sequence

Despite being a popular strategy to overcome drug resistance, co-administration of different treatments may reduce the synergistic benefits of pharmaceuticals in a heterogeneous tumour environment. Since pharmaceuticals have different solubility or cancer-inhibitory effects, it is often advantageous to release drugs from NCD complexes one after the other. Additionally, sequential release may be spatiotemporal, which means that drugs are only released in the recommended order within cancer cells²⁵.

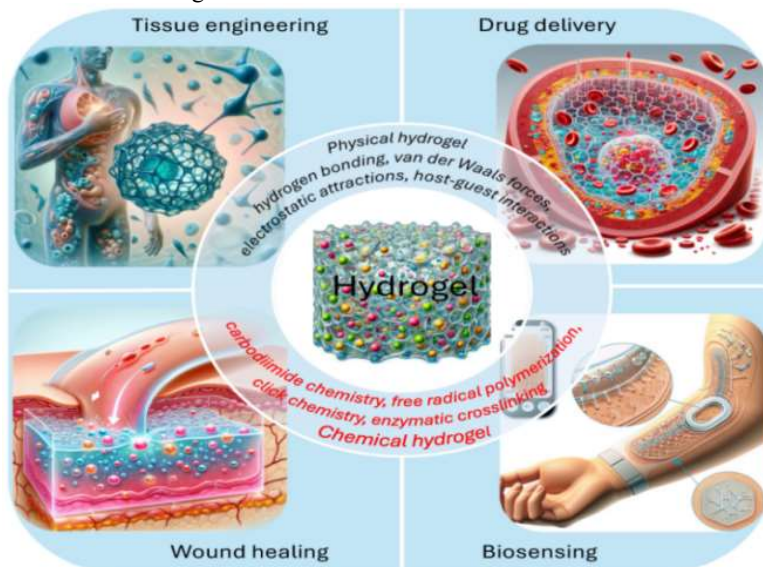


Fig 2: Illustrating the synthesis and versatile biomedical applications of hydrogels, which are categorized based on their crosslinking mechanisms²⁶

Dual-pH-Responsive Nanocarriers for Spatiotemporal Drug Release

Another method for achieving spatiotemporal sequential release is pH control. This prodrug was combined with combretastatin A4 (CA4), a tumour vascular inhibitor that can prevent the development of tumour vasculature by harming the skeletal structure of tumour cells, to create a pH-sensitive poly(ethylene glycol)-polyhistidine (PEG-

Phis) polypeptide. CA4/Pasp-DOX/PEG-Phis is first protonated and then swells in response to tumour extracellular pH conditions (pH 6–7) in the tumour vasculature. Therefore, site-specific sequential drug release from dual-pH-responsive nanocarriers can alter the TME and exert anticancer efficacy against treatment-resistant cancers by promoting the accumulation of anticancer medications in the tumour²⁷.

Table:1 Key Biomedical Applications: Case Studies

Important Biomedical Uses	Utilised Hydrogel	Used Nanoparticles	Formulation Approach
Cancer Treatment	Oxidized alginate Gelatin	Chitosan Pluronic F68	Physical Embedding
	Sodium alginate	Chitosan	Physical Embedding
Wound Healing	N-carboxyethyl chitosan	Mesoporous polydopamine	Physical Embedding
	Polyethylene glycol diacrylate	Chitosan	Layer-by-Layer Assembly
Controlling Infections	Gelatin methacrylate Pluronic F127	PLGA	Layer-by-Layer Assembly
	Silk fibroin	Molybdenum dioxide	Physical Embedding
Transplant Immuno suppression	Cationic peptide	Methoxy poly (ethylene glycol)-poly (ϵ caprolactone)	Physical Embedding

Mathematical Models for Dual-Drug Release

Understanding and predicting the release behaviour of two drugs in a dual-drug delivery system requires mathematical modeling. In hydrogel-nanoparticle composites, each drug may have distinct release mechanisms, routes, and kinetics, necessitating models that can capture this complexity. The models listed below are commonly used: Drug release is assumed to be proportional to the square root of time in the Higuchi model, which is suitable for diffusion-controlled release from hydrogels. zero-order model: The optimal model when a drug's release rate is constant regardless of concentration. targeted but difficult to achieve in dual-drug designs. In dual-drug delivery systems, different models can be used to each drug concurrently, or composite multi-compartment or biexponential models can be used to represent simultaneous and sequential release phases²⁸.

Future prosperity

Nanoparticle-stabilized microemulsions provide a bright future for enhanced oil recovery (EOR) in the petroleum sector. Future research must include the creation of intricate microemulsion compositions. To increase stability and compatibility with reservoir conditions, researchers are attempting to modify the characteristics of nanoparticles, surfactants, and co-surfactants. The creation of dual-drug delivery methods utilising hydrogel-nanoparticle composites has greatly increased precision treatments²⁹. By exploiting the complementary properties of hydrogels and nanoparticles, these systems provide temporal and spatial control over the release of two pharmacologically distinct medicines, enabling sequential or synergistic therapeutic activities. A range of production processes, including emulsion-based nanoparticle encapsulation, in situ crosslinking hydrogels, and microfluidics-enabled architectures, have lately led to a rise in the structural and functional diversity of these systems³⁰.

CONCLUSION

This survey of the literature on microemulsions and nanoparticles might be very helpful in understanding the current state of knowledge in both domains. Microemulsions have been shown to protect labile drugs, control drug release, enhance drug solubility, boost bioavailability, and reduce patient variability. Furthermore, it has been shown that preparations suitable for most administration routes can be made. Microemulsions are used to give high, dependable, and repeatable bioavailability while addressing the issues of highly lipophilic medicinal substances' limited water solubility. To do this, we divided drug release patterns into two groups: ratiometric drug release, which can deliver pharmaceuticals to specific locations by preserving a synergistic drug ratio, and sequential release, which releases drugs across time or space. We also talked about the particular physicochemical methods that are employed to produce these patterns.

Acknowledgment: The authors would like to express their sincere gratitude to all the authors who contributed to this review. We also thank our institution for providing the necessary resources and academic support to complete this article.

Conflicts of Interest: Authors declare no conflict of interest

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