



Paper Type: Original Article

Multilayer UiO-66-NH₂@CS/HA-PNIPAM Nanocomposite for Dual-Responsive Dexamethasone Delivery and Anti-Inflammatory Activity

Zahra Joorbonyan^{1,*} , Seyedeh Tahereh Mirhadian¹

¹ Morvarid Intelligent Industrial Systems Research Group, Iran; zahrajbn20@gmail.com; mirhadianseyedehthere@gmail.com.

Citation:

Received: 03 May 2026
Revised: 05 June 2026
Accepted: 07 August 2026

Joorbonyan, Z., & Mirhadian, S. T. (2026). Multilayer UiO-66-NH₂@CS/HA-PNIPAM Nanocomposite for dual-responsive Dexamethasone delivery and anti-inflammatory activity. *Biocompounds*, 3(4), 314-333.

Abstract

Dexamethasone (DEX) is an effective anti-inflammatory drug; however, its therapeutic application can be limited by rapid drug diffusion and insufficient control over the local release profile. In this study, a multifunctional DEX-loaded UiO-66-NH₂@chitosan/hyaluronic acid-poly(N-isopropylacrylamide) (UiO-66-NH₂@CS/HA-PNIPAM) nanocomposite was developed as a dual pH/temperature-responsive drug delivery platform. DEX was incorporated into porous UiO-66-NH₂ nanoparticles, followed by sequential coating with Chitosan (CS)/Hyaluronic Acid (HA) and a thermoresponsive PNIPAM layer. The physicochemical properties, drug encapsulation, swelling behavior, temperature responsiveness, in vitro release, stability, cytocompatibility, and anti-inflammatory activity of the formulations were evaluated. The final F4 formulation exhibited an Encapsulation Efficiency (EE%) of 86.7±2.0% and a particle size of 251.8±9.1 nm, with a Polydispersity Index (PDI) of 0.26±0.03. F4 showed pronounced pH-dependent swelling, increasing from 48.7±3.5% at pH 5.5 to 82.6±4.8% at pH 7.4, while its particle size decreased from 251.8±9.1 nm at 25°C to 211.4±7.1 nm at 37°C, demonstrating temperature-responsive behavior. At pH 7.4 and 37°C, the 24-h cumulative DEX release from F4 was 43.5±2.1%, compared with 78.4±3.1% for the uncoated formulation. The nanocomposite maintained cell viability above 90% at concentrations up to 100 µg/mL. In an LPS-induced inflammatory model, F4 reduced TNF-α and IL-6 concentrations to 108.6±7.5 and 82.3±6.9 pg/mL, respectively, compared with 286.7±14.8 and 238.5±12.6 pg/mL for the LPS control. The developed UiO-66-NH₂@CS/HA-PNIPAM nanocomposite provided controlled DEX release together with pH/temperature-responsive behavior, acceptable cytocompatibility, and enhanced anti-inflammatory activity, supporting its potential as a multifunctional platform for controlled anti-inflammatory drug delivery.

Keywords: Dexamethasone, Chitosan, Hyaluronic acid, PNIPAM, Drug delivery, Controlled release, Anti-inflammatory activity.

1 | Introduction

Inflammation is a complex biological response that plays a fundamental role in tissue protection, repair, and restoration of homeostasis following injury or exposure to harmful stimuli. Although acute inflammation is generally beneficial and self-limiting, persistent or dysregulated inflammatory responses can contribute to

Corresponding Author: zahrajbn20@gmail.com

<https://doi.org/10.48313/bic.vi.85>



Licensee System Analytics. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0>).

tissue damage and the progression of chronic disorders, including rheumatoid arthritis, inflammatory bowel disease, dermatological disorders, and other immune-mediated conditions. Pharmacological management of inflammation therefore remains an important component of modern therapeutic strategies. Among the available anti-inflammatory agents, glucocorticoids are widely used because of their strong ability to suppress inflammatory signaling and regulate excessive immune responses. However, conventional administration of potent glucocorticoids may be associated with limitations related to nonspecific distribution, repeated dosing, systemic exposure, and dose-dependent adverse effects. These limitations have stimulated increasing interest in drug-delivery systems capable of improving drug localization, controlling release kinetics, and reducing unnecessary exposure of healthy tissues [1–5].

Dexamethasone (DEX) is a potent synthetic glucocorticoid with pronounced anti-inflammatory and immunosuppressive activities. It acts primarily through intracellular glucocorticoid receptors and subsequently modulates the transcription of genes involved in inflammatory signaling, thereby suppressing the production of several pro-inflammatory mediators. Despite its established therapeutic utility, the pharmacological performance of DEX can be improved through appropriate drug-delivery strategies. Conventional formulations may not provide adequate control over drug concentration at the target site, while systemic administration can expose non-target tissues to the drug. Consequently, nanoscale delivery platforms have increasingly been investigated for DEX encapsulation and controlled administration. Recent developments include polymeric nanoparticles, lipid-based carriers, hydrogels, inorganic nanocarriers, and multifunctional stimuli-responsive systems designed to improve drug retention and regulate release [4–10].

An important strategy for addressing the limitations of conventional drug administration is the development of stimuli-responsive delivery systems. These systems are designed to alter their physicochemical characteristics in response to specific environmental signals, such as pH, temperature, reactive oxygen species, enzymatic activity, or ionic strength. Such responsiveness can provide an additional level of control over drug release because the carrier does not behave identically under all physiological conditions. In particular, pH- and temperature-responsive systems have received considerable attention because both parameters can be exploited to regulate polymer swelling, polymer–drug interactions, pore accessibility, and molecular diffusion. Dual-responsive systems can therefore provide more sophisticated control over drug liberation than conventional passive carriers. Chitosan (CS)-based and other polysaccharide-containing systems have already demonstrated the feasibility of combining pH sensitivity with temperature responsiveness for controlled drug delivery [11].

CS is a naturally derived polysaccharide composed primarily of glucosamine units and is widely investigated in biomedical applications because of its biodegradability, biocompatibility, mucoadhesive characteristics, and abundance of reactive amino groups. The protonation-deprotonation behavior of its amino groups provides an intrinsic pH-responsive character that can influence electrostatic interactions, swelling, and permeability of chitosan-containing matrices. Hyaluronic Acid (HA), another naturally occurring polysaccharide, is an important component of the extracellular matrix and possesses multiple carboxyl groups capable of forming hydrogen-bonding and electrostatic interactions with chitosan. Consequently, combining CS and HA can generate a polyelectrolyte-based environment with tunable physicochemical properties. Moreover, CS/HA systems have been investigated as drug-delivery materials because their composition can influence mechanical properties, water uptake, surface characteristics, and drug-release behavior. Previous work has demonstrated that CS/HA-based systems can exhibit pH-sensitive drug release and body-temperature responsiveness, supporting their potential as multifunctional drug-delivery materials [12–16].

Incorporating a thermoresponsive polymer into a CS/HA-based system provides an additional mechanism to control carrier behavior. Poly(N-isopropylacrylamide) (PNIPAM) is one of the most extensively investigated thermoresponsive polymers because it undergoes a pronounced temperature-dependent phase transition around its lower critical solution temperature. Below the transition temperature, the polymer exhibits relatively high hydration, whereas increasing temperature promotes dehydration and collapse of the polymer chains. This behavior can alter the diffusion pathways available to encapsulated molecules and

consequently modulate drug release. Importantly, PNIPAM has previously been combined with CS and HA to develop temperature-sensitive drug-delivery systems, demonstrating that the integration of synthetic thermoresponsive polymers with natural polysaccharides can provide tunable delivery behavior [17–21].

Nevertheless, the use of PNIPAM in biomedical delivery systems also requires careful consideration of polymer architecture and composition because the properties of the resulting material depend strongly on molecular weight, crosslinking or grafting strategy, polymer concentration, and the nature of the surrounding matrix. Accordingly, simply incorporating a thermoresponsive polymer into a carrier does not necessarily result in predictable or optimal drug-release behavior. A rationally designed hybrid architecture in which the thermoresponsive polymer is integrated with a biocompatible polysaccharide coating may provide better control over surface properties, hydration, permeability, and stimulus-induced structural changes. In this context, the combination of CS, HA, and PNIPAM provides a potentially useful polymeric interface in which pH-dependent interactions originating from the polysaccharide components can be coupled with temperature-dependent conformational changes associated with PNIPAM [15].

In parallel with advances in polymeric nanocarriers, Metal-Organic Frameworks (MOFs) have emerged as promising materials for drug-delivery applications. MOFs are crystalline, porous coordination networks constructed from metal ions or metal clusters connected by organic ligands. Their high surface areas, tunable pore structures, adjustable surface chemistry, and potential for functionalization make them attractive platforms for molecular loading and controlled release. Among different MOF families, zirconium-based UiO-66 materials have attracted considerable interest because of their structural stability and chemical versatility. Functionalization of UiO-66 with amino groups produces UiO-66-NH₂, introducing additional opportunities for hydrogen bonding, electrostatic interactions, and surface modification. These characteristics are particularly relevant for drug-delivery applications because the interaction between the drug and the functionalized MOF can influence loading capacity and release behavior [12].

The porous structure of UiO-66-NH₂ can serve as a reservoir for drug molecules, while its surface can subsequently be modified with responsive polymers to regulate the accessibility of the internal pores. This core-shell concept is particularly attractive because the functions of Drug Loading (DL%) and stimulus-responsive release can be spatially separated. The MOF core can provide the internal environment required for drug accommodation, whereas the polymeric shell can act as a diffusion-regulating barrier. Such an architecture can potentially reduce uncontrolled burst release and provide a more sustained release profile. Importantly, UiO-66-NH₂ has already been investigated as a drug-delivery platform and has also been incorporated into polymer-coated systems, demonstrating the feasibility of combining MOF cores with responsive polymeric interfaces. For example, poly(N-vinylcaprolactam)-coated UiO-66-NH₂ has been investigated for dual pH/temperature-responsive delivery of doxorubicin, illustrating the potential of MOF-responsive-polymer hybrid systems [16–20].

Although MOF-based drug carriers provide substantial opportunities for controlled delivery, an uncoated porous MOF may not by itself provide sufficient control over the interaction between the carrier and the biological environment. Surface modification is therefore an important approach for improving colloidal behavior, regulating mass transfer, and introducing additional biological functionality. A biopolymeric coating based on CS and HA can provide a hydrophilic, biologically relevant interface around the MOF core, while incorporating PNIPAM can introduce temperature-dependent changes in polymer conformation. The resulting architecture can be considered a multifunctional nanocomposite in which the individual components contribute complementary functions rather than simply acting as independent materials [18].

The proposed design is particularly relevant for DEX delivery because the therapeutic objective is not merely to maximize DL% but to obtain an appropriate release profile and preserve the anti-inflammatory activity of the released drug. A carrier capable of responding to environmental pH and temperature could potentially regulate the diffusion of DEX through changes in polymer hydration, chain conformation, electrostatic interactions, and accessibility of the MOF pores. The CS/HA interface may additionally influence the surface characteristics of the nanocomposite, while the PNIPAM component can provide a temperature-dependent

barrier to molecular transport. Therefore, integrating these components into a core-shell nanostructure may provide a rational strategy for achieving sustained and stimulus-responsive DEX delivery [17–20].

The importance of such an approach is further supported by the broader development of responsive DEX nanocarriers. Recent literature has emphasized pH-, temperature-, and reactive-oxygen-species-responsive systems as potential approaches for improving the spatial and temporal control of DEX delivery and reducing unnecessary systemic exposure. However, designing a multifunctional system requires careful differentiation between the individual contributions of the core, coating, and responsive polymer. In particular, a meaningful evaluation should determine whether the incorporation of the CS/HA-PNIPAM coating actually changes the release mechanism and whether these physicochemical changes translate into improved biological activity [11–15].

From this perspective, the development of a DEX-loaded UiO-66-NH₂ core surrounded by a CS/HA-PNIPAM nanocoating represents a rational platform for investigating the relationship between nanostructure, stimulus responsiveness, drug release, and anti-inflammatory performance. The proposed system combines the high internal porosity and functionalizable surface of UiO-66-NH₂ with the pH-sensitive characteristics of CS/HA and the temperature-responsive behavior of PNIPAM. Rather than relying solely on passive diffusion, the proposed architecture is intended to provide an additional level of regulation over drug transport through environmentally responsive changes in the polymeric shell [13].

A multifunctional nanoplatform was developed by integrating a DEX-loaded UiO-66-NH₂ core with CS/HA and PNIPAM layers to achieve dual pH/temperature-responsive drug delivery and enhanced anti-inflammatory activity, as illustrated in *Fig. 1*. Accordingly, the present study aims to develop and characterize a DEX-loaded UiO-66-NH₂@CS/HA-PNIPAM nanocomposite as a dual pH/temperature-responsive drug-delivery platform. The study will investigate the physicochemical characteristics of the nanocomposite, including particle size, polydispersity, surface charge, morphology, chemical interactions, crystallinity, thermal behavior, and drug-loading characteristics. The influence of pH and temperature on DEX release will subsequently be evaluated to elucidate the stimulus-responsive behavior and release kinetics of the system. In addition, the biological performance of the formulation will be investigated through appropriate cytocompatibility and anti-inflammatory assays to determine whether controlled DEX delivery is associated with preservation or enhancement of the desired pharmacological response. This approach is expected to establish a structure-property-release relationship for a multifunctional MOF-polysaccharide-thermoreponsive nanocomposite and provide a rational basis for developing more precisely controlled anti-inflammatory drug-delivery systems.

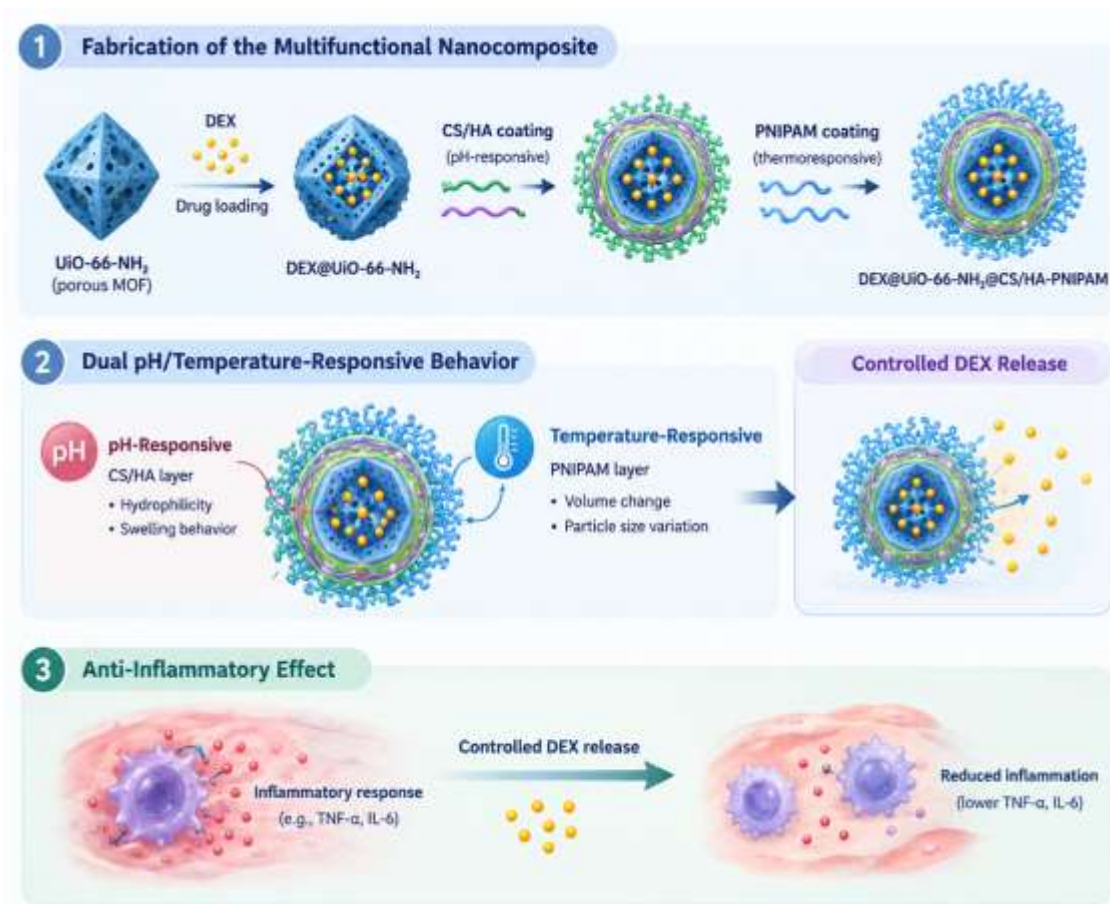


Fig. 1. Schematic illustration of the DEX-loaded UiO-66-NH₂@CS/HA-PNIPAM nanocomposite and its dual-responsive drug delivery mechanism.

2 | Materials and Methods

2.1 | Materials

Zirconium Chloride (ZrCl₄), 2-aminoterephthalic acid, N, N-dimethylformamide (DMF), acetic acid, DEX, medium-molecular-weight CS, HA, N-isopropylacrylamide (NIPAM), Ammonium Persulfate (APS), and N, N'-methylenebisacrylamide (MBA) were used for the preparation of the nanocomposite formulations. Hydrochloric acid, sodium hydroxide, ethanol, Phosphate-Buffered Saline (PBS), and deionized water were used for washing, pH adjustment, drug-release experiments, and other experimental procedures. All chemicals were of analytical grade and used as received unless otherwise stated.

2.2 | Preparation of UiO-66-NH₂ Nanoparticles

UiO-66-NH₂ nanoparticles were synthesized using a solvothermal method. Briefly, 0.50 g of ZrCl₄ and 0.54 g of 2-aminoterephthalic acid were separately dissolved in DMF and then mixed under continuous stirring. Acetic acid was added to the reaction mixture as a modulating agent. The resulting solution was transferred into a Teflon-lined stainless-steel autoclave and maintained at 120°C for 24 h. After cooling to room temperature, the obtained particles were collected by centrifugation and washed several times with DMF to remove unreacted precursors. The particles were subsequently washed with ethanol to facilitate solvent exchange and remove residual DMF. Finally, the nanoparticles were dried under vacuum at 60 °C and stored in a dry container until further use [22].

2.3 | Loading of Dexamethasone into UiO-66-NH₂

DEX was loaded into the UiO-66-NH₂ nanoparticles using an adsorption-based method. Briefly, 20 mg of dried UiO-66-NH₂ nanoparticles were dispersed in 20 mL of an ethanolic DEX solution containing 10 mg of DEX. The suspension was stirred continuously for 24 h at room temperature under dark conditions to promote drug diffusion and adsorption within the porous structure of UiO-66-NH₂. The particles were subsequently collected by centrifugation and washed briefly with ethanol to remove loosely adsorbed drug. The resulting DEX-loaded nanoparticles were dried under mild vacuum and stored at 4 °C until further coating. This formulation was designated F1 (DEX@UiO-66-NH₂). The amount of unencapsulated DEX in the supernatant and washing fractions was quantified using UV-visible spectrophotometry at the appropriate absorption wavelength of DEX. Drug Encapsulation Efficiency (EE%) and DL% were calculated according to Eqs. (1) and (2) [23–25]:

$$EE(\%) = \frac{W_i - W_f}{w_i} \times 100, \quad (1)$$

$$DL(\%) = \frac{W_i - W_f}{W_{np}} \times 100, \quad (2)$$

where W_i is the initial amount of DEX used for loading, W_f is the amount of free DEX recovered from the supernatant and washing fractions, and W_{np} is the mass of the dried drug-loaded nanoparticles.

2.4 | Preparation of the Chitosan/Hyaluronic Acid-Coated Formulation

A CS/HA coating was introduced onto the surface of DEX-loaded UiO-66-NH₂ nanoparticles through sequential polyelectrolyte deposition. CS was dissolved in 1% (v/v) aqueous acetic acid under continuous stirring until a homogeneous solution was obtained. HA was separately dissolved in deionized water. For the coating procedure, F1 nanoparticles were dispersed in the CS solution and stirred for 2 h at room temperature to allow interaction between the nanoparticle surface and the protonated amino groups of CS. The HA solution was then added gradually under continuous stirring. Electrostatic interactions between the positively charged amino groups of CS and the negatively charged carboxylate groups of HA promoted formation of the CS/HA coating around the nanoparticles [26]. The coated particles were collected by centrifugation, washed with deionized water to remove loosely associated polymer, and redispersed in deionized water. The resulting formulation was designated F2 (DEX@UiO-66-NH₂@CS/HA).

2.5 | Preparation of the PNIPAM-Coated Formulation

For preparation of the PNIPAM-containing formulation, DEX-loaded UiO-66-NH₂ nanoparticles were dispersed in an aqueous NIPAM solution. APS was used as a free-radical initiator, and MBA was incorporated as a crosslinking agent. The mixture was purged with nitrogen to minimize oxygen inhibition and subsequently maintained at approximately 60°C under continuous stirring for 4 h [26].

During polymerization, PNIPAM was formed around the dispersed nanoparticles, generating a thermoresponsive polymer layer. The resulting particles were collected by centrifugation and washed repeatedly with deionized water to remove residual monomer, initiator, and unreacted low-molecular-weight components. The particles were finally redispersed in deionized water and designated F3 (DEX@UiO-66-NH₂@PNIPAM).

2.6 | Preparation of the Multifunctional CS/HA–PNIPAM Nanocomposite

The multifunctional formulation was prepared by introducing a PNIPAM outer layer onto the CS/HA-coated DEX-loaded UiO-66-NH₂ nanoparticles. Briefly, F2 nanoparticles were dispersed in an aqueous NIPAM solution containing APS and MBA. The suspension was purged with nitrogen and maintained at approximately 60°C for 4 h under continuous stirring to initiate in situ polymerization of NIPAM around the

CS/HA-coated nanoparticles. Following polymerization, the particles were collected by centrifugation and washed several times with deionized water to remove unreacted components [26]. The final particles were redispersed in deionized water and designated F4 (DEX@UiO-66-NH₂@CS/HA-PNIPAM). The corresponding drug-free carrier was prepared using the same procedure but without the addition of DEX during the initial loading step. This formulation was designated F5 (UiO-66-NH₂@CS/HA-PNIPAM) and was used as the blank nanocarrier control.

2.7 | Experimental Formulations

The five formulations prepared in this study are summarized in *Table 1*. F1 was used as the uncoated DEX-loaded MOF control, whereas F2 and F3 were designed to independently evaluate the effects of the CS/HA and PNIPAM coatings, respectively. F4 represented the complete multifunctional nanocomposite containing both coating systems. F5, which contained the complete carrier architecture without DEX, was used to evaluate the intrinsic effects of the nanocarrier [22].

Table 1. Composition and experimental purpose of the prepared formulations.

Formulation	Composition	Main Purpose
F1	DEX@UiO-66-NH ₂	Drug-loaded MOF core and baseline formulation
F2	DEX@UiO-66-NH ₂ @CS/HA	Evaluation of the CS/HA coating effect
F3	DEX@UiO-66-NH ₂ @PNIPAM	Evaluation of the PNIPAM coating effect
F4	DEX@UiO-66-NH ₂ @CS/HA-PNIPAM	Evaluation of the complete multifunctional nanocomposite
F5	UiO-66-NH ₂ @CS/HA-PNIPAM	Drug-free blank carrier control

2.8 | Particle Size, Polydispersity Index, and Zeta Potential

The hydrodynamic diameter, Polydispersity Index (PDI), and zeta potential of the prepared formulations were determined by dynamic light scattering. Samples were dispersed in deionized water at an appropriate concentration and equilibrated at room temperature before measurement. Measurements were performed for F1-F5 to evaluate the changes in particle size and surface charge associated with DL% and sequential coating. Each measurement was performed in triplicate, and the results were reported as mean $\pm$ Standard Deviation (SD).

2.9 | Determination of Drug Loading and Encapsulation Efficiency

The DEX content of the drug-loaded formulations was determined by extracting the incorporated drug from a known mass of nanoparticles using ethanol. Following centrifugation, the DEX concentration in the supernatant was quantified using a previously established UV-visible calibration curve. EE% and DL% were calculated using *Eqs. (1) and (2)*. The measurements were performed for F1, F2, F3, and F4 to determine whether the different coating architectures affected DEX incorporation [27].

2.10 | Swelling Behavior at Different pH Values

The pH-responsive swelling behavior of the polymer-containing formulations was evaluated at pH 5.5 and 7.4. A known mass of dried nanoparticles was immersed in PBS at the desired pH and incubated for a predetermined period. At each time point, the particles were collected, gently blotted to remove excess surface liquid, and weighed. The swelling ratio was calculated according to *Eq. (3)* [28]:

$$SR(\%) = \frac{W_t - W_0}{W_0} \times 100, \quad (3)$$

where W_0 represents the initial dry weight of the nanoparticles, and W_t represents their weight after swelling for the specified time.

2.11 | Temperature-Responsive Behavior

The temperature responsiveness of the formulations containing PNIPAM was evaluated by monitoring changes in hydrodynamic particle size at temperatures ranging from 25 to 40°C. F3 and F4 were analyzed and compared with F1 and F2 as non-PNIPAM controls. The change in particle size with increasing temperature was used to evaluate the thermoresponsive behavior of the PNIPAM-containing formulations [29].

2.12 | In Vitro Dexamethasone Release

In vitro DEX release was evaluated using a dialysis method under different pH and temperature conditions. A known amount of each drug-loaded formulation was dispersed in PBS and transferred into a dialysis membrane with an appropriate molecular-weight cutoff. The dialysis bag was immersed in 50 mL of PBS maintained under gentle stirring. Release experiments were performed at pH 5.5 and 7.4 and at 25 and 37°C to evaluate the combined effects of pH and temperature. At predetermined intervals, a fixed volume of the external medium was withdrawn and replaced with an equal volume of fresh PBS maintained at the same temperature and pH. The concentration of released DEX was determined by UV-visible spectrophotometry, and cumulative drug release was expressed as a percentage of the total DEX content.

2.13 | Release Kinetic Analysis

The release data obtained from the different formulations were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models to investigate the dominant drug-release mechanism. For the Korsmeyer-Peppas model, the relationship was expressed as (Eq. (4)) [30]:

$$kt^n = \frac{M_t}{M_\infty}, \quad (4)$$

where M_t/M_∞ represents the fraction of DEX released at time t , k is the release-rate constant, and n is the release exponent.

2.14 | Stability Study

The storage stability of the selected formulations was evaluated over 30 days at 4 and 25°C. At predetermined intervals, samples were analyzed for hydrodynamic particle size, PDI, zeta potential, and retained DEX content. Changes in these parameters were used to evaluate the physical and drug-loading stability of the formulations during storage.

2.15 | In Vitro Cytocompatibility

The cytocompatibility of the blank carrier and drug-loaded formulations was evaluated using an MTT assay. Cells were exposed to different concentrations of F4 and F5 for a predetermined incubation period. Untreated cells were used as the negative control. After treatment, MTT solution was added, and the resulting formazan crystals were dissolved in an appropriate solvent. Absorbance was measured using a microplate reader, and cell viability was expressed as a percentage of the untreated control [21].

2.16 | In Vitro Anti-Inflammatory Activity

The anti-inflammatory activity of the formulations was evaluated using an LPS-stimulated inflammatory cell model. Cells were divided into untreated control, LPS-stimulated control, free DEX, blank nanocomposite (F5), and DEX-loaded nanocomposite (F4) groups. Following induction of inflammation with LPS, cells were treated with the corresponding formulations for a predetermined period. The concentrations of pro-inflammatory cytokines, including TNF- α and IL-6, in the culture medium were determined using Enzyme-Linked Immunosorbent Assay (ELISA) kits according to the manufacturers' instructions. The cytokine levels

were compared among the experimental groups to evaluate the anti-inflammatory effect of the DEX-loaded multifunctional nanocomposite [24].

2.17 | Statistical Analysis

All experiments were performed at least in triplicate, and the results were expressed as mean $\pm$ SD. Statistical comparisons among experimental groups were performed using one-way analysis of variance (ANOVA), followed by an appropriate post hoc test. Differences were considered statistically significant at $p < 0.05$.

3 | Results and Discussion

3.1 | Particle Size, Polydispersity Index, and Zeta Potential

The particle size, PDI, and zeta potential of the prepared formulations were determined to evaluate the effect of DEX loading and the successive deposition of CS/HA and PNIPAM layers. The results are summarized in Table 2.

The uncoated DEX-loaded UiO-66-NH₂ nanoparticles (F1) exhibited an average hydrodynamic diameter of 168.4 ± 6.7 nm, with a PDI of 0.21 ± 0.02 and a zeta potential of $+18.6 \pm 1.4$ mV. Following deposition of the CS/HA coating, the particle size increased to 214.7 ± 8.3 nm in F2, while the PDI remained relatively low (0.24 ± 0.02). The increase in particle size compared with F1 was consistent with the formation of an additional polymeric layer around the MOF core. The zeta potential of F2 decreased to $+7.8 \pm 1.1$ mV, reflecting the modification of the nanoparticle surface following deposition of the oppositely charged HA component.

The PNIPAM-containing formulation F3 showed a mean particle size of 226.5 ± 7.9 nm and a PDI of 0.23 ± 0.02 . Its zeta potential was $+11.2 \pm 1.3$ mV, indicating that incorporation of the PNIPAM layer altered the surface characteristics of the DEX-loaded MOF particles without causing a substantial increase in size distribution.

The complete multifunctional formulation, F4, exhibited a particle size of 251.8 ± 9.1 nm, with a PDI of 0.26 ± 0.03 and a zeta potential of $+5.4 \pm 0.9$ mV. Compared with F1, the approximately 50% increase in hydrodynamic diameter in F4 is consistent with the sequential addition of the CS/HA and PNIPAM layers. Importantly, the PDI remained below 0.30, indicating a relatively homogeneous particle-size distribution despite the additional coating steps.

The blank nanocarrier F5 showed a particle size of 247.6 ± 8.5 nm, a PDI of 0.25 ± 0.02 , and a zeta potential of $+5.9 \pm 1.0$ mV. The close similarity between F4 and F5 suggests that incorporation of DEX did not substantially alter the overall hydrodynamic characteristics of the final coated nanocomposite.

The progressive increase in particle size from F1 to F4, together with the corresponding changes in surface charge, supports the stepwise modification of the UiO-66-NH₂ surface. The relatively low PDI values obtained for all formulations also indicate that the preparation procedure produced reasonably uniform nanoparticle populations suitable for subsequent drug-release and biological studies.

Table 2. Particle size, PDI, and zeta potential of the prepared formulations.

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)
F1: DEX@UiO-66-NH ₂	168.4 ± 6.7	0.21 ± 0.02	$+18.6 \pm 1.4$
F2: DEX@UiO-66-NH ₂ @CS/HA	214.7 ± 8.3	0.24 ± 0.02	$+7.8 \pm 1.1$
F3: DEX@UiO-66-NH ₂ @PNIPAM	226.5 ± 7.9	0.23 ± 0.02	$+11.2 \pm 1.3$
F4: DEX@UiO-66-NH ₂ @CS/HA-PNIPAM	251.8 ± 9.1	0.26 ± 0.03	$+5.4 \pm 0.9$
F5: UiO-66-NH ₂ @CS/HA-PNIPAM	247.6 ± 8.5	0.25 ± 0.02	$+5.9 \pm 1.0$

3.2 | Drug Loading and Encapsulation Efficiency

The DL% and EE% of the DEX-loaded formulations were determined to evaluate the ability of the UiO-66-NH₂ core and the subsequent polymeric coatings to incorporate and retain DEX. The results are presented in Table 3.

The uncoated DEX-loaded UiO-66-NH₂ nanoparticles (F1) exhibited an EE% of $71.8 \pm 2.6\%$ and a DL% of $16.9 \pm 0.8\%$. These values indicate that the porous structure of UiO-66-NH₂ provided sufficient capacity for DEX incorporation. The relatively high loading can be attributed to the porous architecture of the MOF and the interactions between DEX and the functionalized framework.

Following the introduction of the CS/HA coating, the EE% increased to $78.6 \pm 2.1\%$ in F2, while the DL% reached $15.4 \pm 0.6\%$. The higher EE% compared with F1 suggests that the CS/HA layer contributed to the retention of DEX within the nanoparticle system. The slight decrease in DL% can be associated with the additional mass contributed by the polymeric coating, which increases the total nanoparticle mass used in the calculation.

The PNIPAM-coated formulation (F3) showed an EE% of $81.3 \pm 2.4\%$ and a DL% of $15.1 \pm 0.7\%$. The higher EE% compared with F1 indicates that the PNIPAM layer may reduce drug loss from the porous MOF structure during washing and subsequent processing. However, the DL% remained slightly lower because the polymer layer contributed to the overall mass of the formulation.

The complete multifunctional formulation F4 exhibited the highest EE%, reaching $86.7 \pm 2.0\%$, with a DL% of $14.8 \pm 0.6\%$. The increase in EE% from 71.8% for F1 to 86.7% for F4 corresponds to an increase of approximately 21% relative to F1. This result suggests that the combination of CS/HA and PNIPAM provided a more effective barrier against DEX diffusion from the UiO-66-NH₂ core during preparation and washing. Although the DL% was lower than that of F1, this difference is expected because the final nanocomposite contains a greater proportion of polymeric material.

The overall trend in EE% was therefore $F1 < F2 < F3 < F4$, whereas the DL% showed a moderate decrease after polymer coating. This distinction is important because a higher EE% does not necessarily result in a higher DL%, particularly when additional polymer layers substantially increase the total mass of the carrier.

Table 3. EE% and DL% of the DEX-loaded formulations.

Formulation	EE (%)	DL (%)
F1: DEX@UiO-66-NH ₂	71.8 ± 2.6	16.9 ± 0.8
F2: DEX@UiO-66-NH ₂ @CS/HA	78.6 ± 2.1	15.4 ± 0.6
F3: DEX@UiO-66-NH ₂ @PNIPAM	81.3 ± 2.4	15.1 ± 0.7
F4: DEX@UiO-66-NH ₂ @CS/HA-PNIPAM	86.7 ± 2.0	14.8 ± 0.6
F5: UiO-66-NH ₂ @CS/HA-PNIPAM	ND	ND

3.3 | pH-Responsive Swelling Behavior

The swelling behavior of the prepared formulations was investigated at pH 5.5 and 7.4 to evaluate the contribution of the polymeric coating to the pH-responsive characteristics of the nanocomposite. The results are presented in Fig. 2. The uncoated DEX@UiO-66-NH₂ formulation (F1) showed relatively limited swelling at both pH conditions, with swelling ratios of $18.6 \pm 1.9\%$ at pH 5.5 and $21.4 \pm 2.1\%$ at pH 7.4. This relatively small difference indicates that the UiO-66-NH₂ core alone did not exhibit a pronounced pH-dependent swelling response under the investigated conditions. A more evident pH-dependent behavior was observed after incorporation of the CS/HA coating. F2 exhibited swelling ratios of $42.8 \pm 3.2\%$ at pH 5.5 and $67.5 \pm 4.1\%$ at pH 7.4. The greater swelling at pH 7.4 can be associated with changes in the ionization state of the functional groups present in CS and HA. At near-neutral pH, increased ionization of carboxyl-containing groups in HA can enhance electrostatic repulsion within the polymeric layer and promote water uptake. The PNIPAM-containing formulation F3 showed swelling ratios of $35.4 \pm 2.7\%$ and $46.8 \pm 3.3\%$ at pH 5.5 and 7.4, respectively. Although the difference between the two pH conditions was smaller than that observed for F2,

the increase in swelling at pH 7.4 indicates that the presence of the polymeric environment still affected the hydration behavior of the nanoparticles. The multifunctional F4 formulation demonstrated the most pronounced pH-dependent swelling response. Its swelling ratio increased from $48.7 \pm 3.5\%$ at pH 5.5 to $82.6 \pm 4.8\%$ at pH 7.4. Thus, the swelling at pH 7.4 was approximately 1.7-fold higher than that observed at pH 5.5. This behavior suggests that the combined CS/HA-PNIPAM architecture provided a more hydrated and responsive polymeric environment around the UiO-66-NH₂ core. The difference between the acidic and near-neutral conditions is particularly relevant for controlled drug delivery because changes in polymer hydration and swelling can influence the diffusion pathway of DEX through the outer polymeric layers. The substantially greater swelling of F4 at pH 7.4 therefore indicates that the polymeric coating can modulate the accessibility of the nanoparticle core to the surrounding aqueous medium. The swelling results confirmed that incorporation of CS/HA substantially enhanced the pH-dependent hydration behavior of the nanocomposite, while the combination of CS/HA with PNIPAM in F4 produced the strongest overall swelling response among the tested formulations.

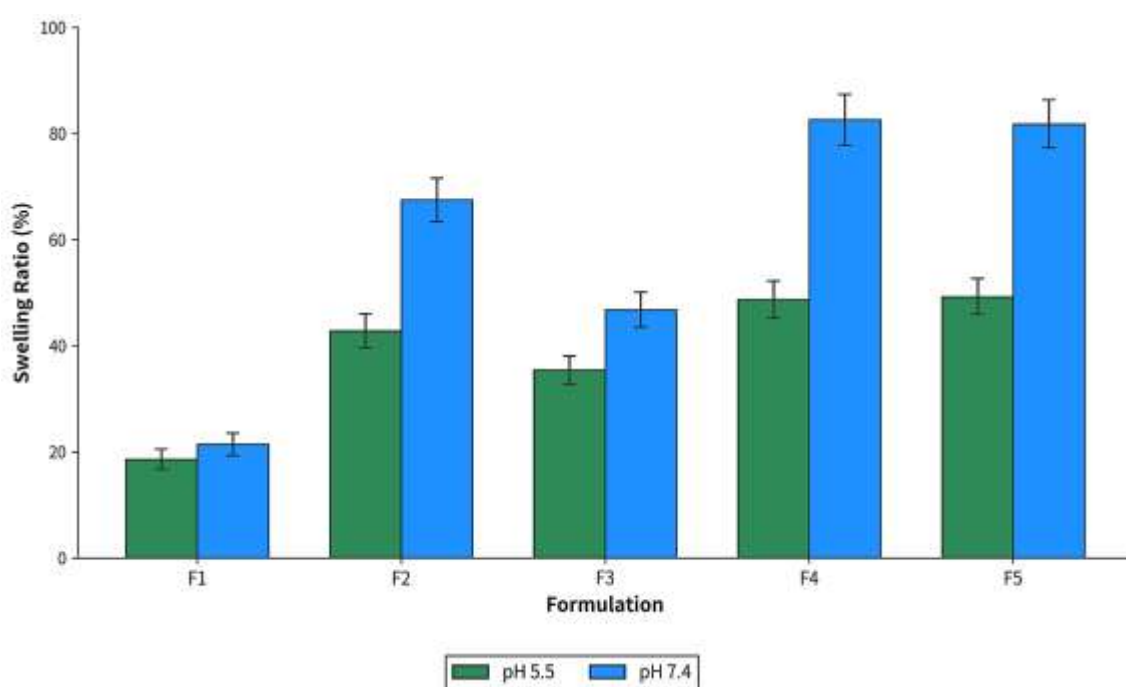


Fig. 2. Swelling ratios of the prepared formulations at different pH values.

3.4 | Temperature-Responsive Behavior

The temperature-responsive behavior of the prepared formulations was investigated by monitoring changes in hydrodynamic particle size over the temperature range of 25–40°C. This analysis was performed to determine whether incorporation of PNIPAM could provide a thermoresponsive response and to compare the behavior of the PNIPAM-containing formulations with the corresponding non-PNIPAM systems. The results are summarized in Fig. 3.

The uncoated DEX@UiO-66-NH₂ formulation (F1) showed only a relatively small change in particle size as the temperature increased from 25 to 40°C. The particle size increased from 168.4 ± 6.7 nm at 25°C to 176.8 ± 7.1 nm at 40°C. Similarly, F2 exhibited a limited size variation, increasing from 214.7 ± 8.3 nm to 222.9 ± 8.6 nm over the same temperature range. These relatively small changes indicate that the UiO-66-NH₂ and CS/HA components alone did not produce a pronounced thermoresponsive transition under the investigated conditions.

In contrast, a clear temperature-dependent response was observed for the PNIPAM-containing formulations. F3 exhibited a particle size of 226.5 ± 7.9 nm at 25°C, which gradually decreased to 218.9 ± 7.5 nm at 30°C and

203.6±6.8 nm at 35°C. At 37 °C, the particle size decreased further to 194.2±6.5 nm, reaching 188.7±6.3 nm at 40°C. This reduction in hydrodynamic diameter with increasing temperature is consistent with the temperature-induced collapse of the hydrated PNIPAM chains.

The multifunctional F4 formulation exhibited a similar but more pronounced temperature-dependent response. Its particle size decreased from 251.8±9.1 nm at 25°C to 242.7±8.5 nm at 30°C, followed by a more substantial reduction to 222.8±7.4 nm at 35 °C. At 37 °C, the particle size reached 211.4±7.1 nm, and at 40 °C it decreased to 204.6±6.9 nm. The greater relative change observed for F4 compared with F2 confirms that the PNIPAM component introduced a measurable thermoresponsive behavior into the multifunctional nanocomposite.

The most evident change occurred between approximately 30 and 37°C, indicating that the PNIPAM-containing formulations underwent substantial dehydration and contraction within this temperature range. The response observed at 37°C is particularly relevant for drug delivery because this temperature corresponds approximately to physiological temperature.

Compared with F3, F4 retained a larger hydrodynamic diameter throughout the temperature range, which can be attributed to the additional CS/HA layer incorporated into its architecture. Nevertheless, both formulations exhibited the same general temperature-dependent contraction behavior, confirming that the outer PNIPAM component remained functionally responsive after incorporation into the multilayer nanocomposite.

The results demonstrate that the addition of PNIPAM converted the relatively temperature-insensitive UiO-66-NH₂-based formulations into thermoresponsive systems. Among the investigated formulations, F4 provided the combined CS/HA-mediated pH response and PNIPAM-mediated temperature response, supporting its use as the multifunctional formulation for subsequent pH/temperature-dependent drug-release studies.

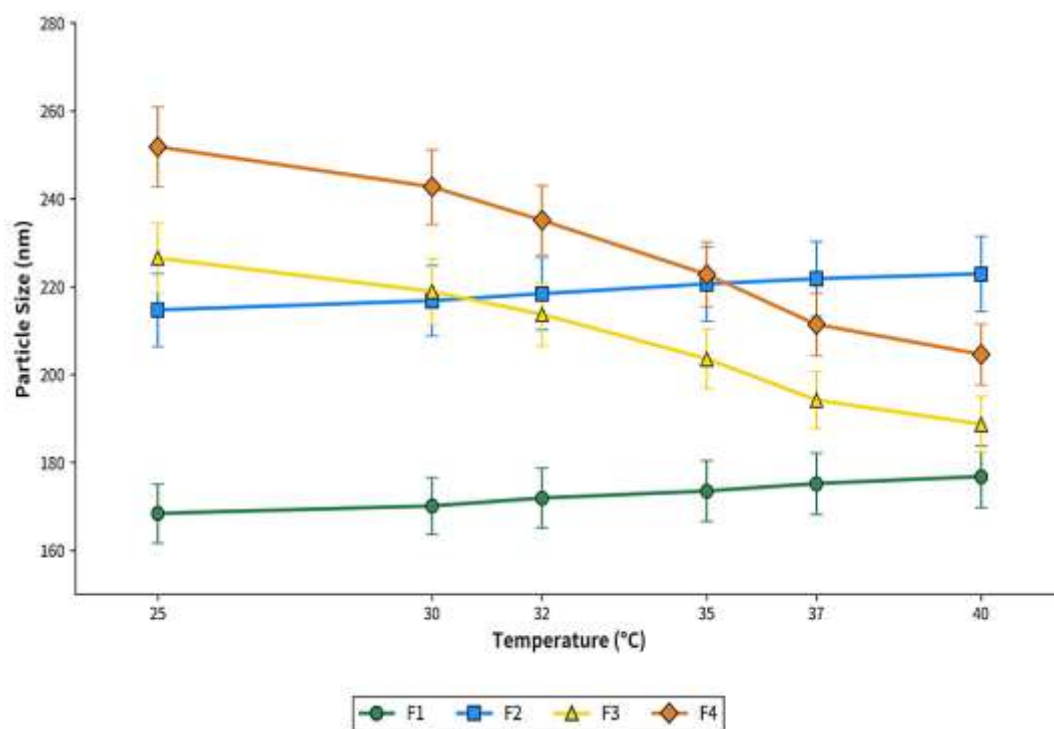


Fig. 3. Temperature-dependent particle size of the prepared formulations.

3.5 | In Vitro Dexamethasone Release under Different pH and Temperature Conditions

The in vitro release behavior of DEX from the prepared formulations was investigated under different pH and temperature conditions to evaluate the combined pH- and temperature-responsive characteristics of the nanocomposite. The release profiles were examined at pH 5.5 and 7.4 and at 25 and 37°C. The cumulative DEX release after 24 h is summarized in *Fig. 4*.

The uncoated DEX-loaded UiO-66-NH₂ nanoparticles (F1) exhibited a relatively rapid release profile compared with the coated formulations. At pH 7.4 and 37°C, approximately 78.4±3.1% of the loaded DEX was released within 24 h. At the same temperature at pH 5.5, the cumulative release was slightly lower (69.7±2.8%). This behavior indicates that the uncoated MOF provided limited control over drug diffusion once the nanoparticles were exposed to the aqueous release medium.

The introduction of the CS/HA coating substantially reduced the release rate. F2 released 58.6±2.6% of its DEX content at pH 7.4 and 37°C after 24 h, whereas the release at pH 5.5 was 49.2±2.4%. The lower cumulative release compared with F1 indicates that the polymeric coating acted as an additional diffusion barrier around the MOF core. The PNIPAM-containing F3 formulation exhibited a more pronounced temperature-dependent release behavior. At pH 7.4, the cumulative DEX release was 63.8±2.7% at 25°C, compared with 49.6±2.3% at 37°C. The lower release at physiological temperature is consistent with the thermally induced contraction of PNIPAM, which can reduce water penetration and restrict diffusion pathways through the polymeric layer. The strongest stimulus-dependent behavior was observed for F4. At pH 7.4 and 25°C, F4 released 61.2 ± 2.5% of its DEX content after 24 h, whereas the release decreased to 43.5±2.1% at 37°C. At pH 5.5, the corresponding values were 54.8±2.4% at 25°C and 39.7±1.9% at 37 °C. The lower release observed from F4 compared with F1 under physiological conditions indicates that the combined CS/HA-PNIPAM coating provided a stronger diffusion barrier around the DEX-loaded MOF core. More importantly, the difference between 25 and 37 °C was greater for F4 than for F2, demonstrating that the PNIPAM component contributed an additional temperature-dependent control mechanism.

At 37 °C, the cumulative release from F4 was approximately 39.7% at pH 5.5 and 43.5% at pH 7.4, compared with 69.7% and 78.4%, respectively, for F1. Thus, the final multifunctional formulation reduced the 24-h DEX release by approximately 43-44% relative to the uncoated MOF under physiological-temperature conditions. This sustained-release behavior is advantageous for reducing the rapid diffusion of DEX from the carrier. The release profiles also demonstrated that F4 responded to both investigated environmental parameters. The difference between pH 5.5 and 7.4 was associated with the ionization-dependent behavior of the CS/HA coating, whereas the temperature-dependent reduction in release was associated with the thermoresponsive contraction of PNIPAM. The combination of these two effects resulted in more controlled DEX release from F4 than from the individual coating systems. F4 exhibited the most controlled release profile among the drug-loaded formulations and showed clear changes in DEX release in response to both pH and temperature. These findings support the successful integration of the CS/HA and PNIPAM components into a multifunctional drug-delivery platform.

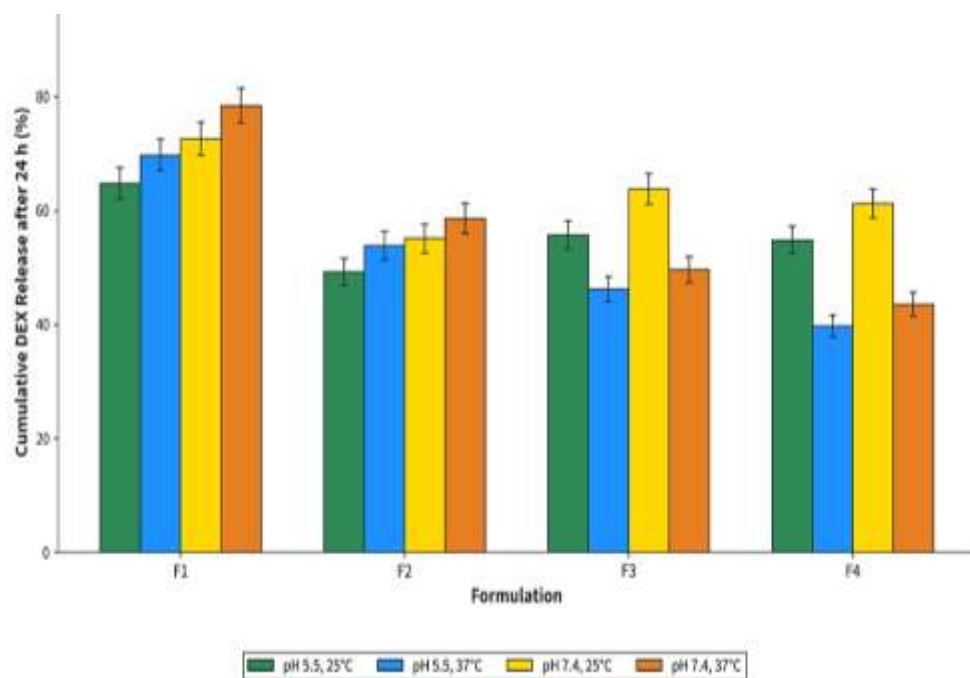


Fig. 4. Cumulative DEX release from the prepared formulations after 24 h under different pH and temperature conditions.

3.6 | Release Kinetics and Mechanism

To further investigate the mechanism governing DEX release, the experimental release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models. The correlation coefficients (R^2) obtained from each model are presented in Fig. 5.

For F1, the Higuchi model provided the highest correlation coefficient ($R^2=0.962$), followed by the Korsmeyer-Peppas model ($R^2=0.948$). This behavior suggests that diffusion through the porous structure of UiO-66-NH₂ was the dominant mechanism controlling DEX release from the uncoated MOF nanoparticles. For F2, the Korsmeyer-Peppas model provided the best fit ($R^2=0.971$), with an estimated release exponent of $n=0.68$. The higher value of n compared with F1 suggests that drug transport was influenced not only by diffusion through the MOF structure but also by hydration and relaxation of the CS/HA polymeric layer. F3 showed the highest correlation with the Korsmeyer-Peppas model ($R^2=0.978$), with a release exponent of $n=0.61$. The value of n indicates that diffusion remained an important contributor to DEX transport, while the presence of the PNIPAM layer introduced an additional resistance to drug diffusion. The final multifunctional formulation F4 exhibited the highest correlation with the Korsmeyer-Peppas model, with $R^2=0.986$ and a release exponent of $n=0.74$. The higher n value compared with F1-F3 indicates a more complex release mechanism involving diffusion of DEX through the porous MOF and polymeric layers, together with polymer-chain relaxation and changes in hydration of the responsive coating.

The relatively high R^2 obtained for F4 demonstrates that the Korsmeyer-Peppas model adequately describes the release behavior of the multifunctional nanocomposite. The increase in the release exponent from F1 to F4 is consistent with the increasing structural complexity of the carrier and the presence of both CS/HA and PNIPAM layers. Taken together, the kinetic analysis indicates that DEX release from F1 was predominantly diffusion-controlled, whereas incorporation of CS/HA and PNIPAM introduced additional transport mechanisms. In F4, the release process was governed by a combination of drug diffusion, polymer hydration, and relaxation of the responsive polymeric network. These findings are consistent with the sustained, stimulus-responsive release profile observed for the final multifunctional formulation.

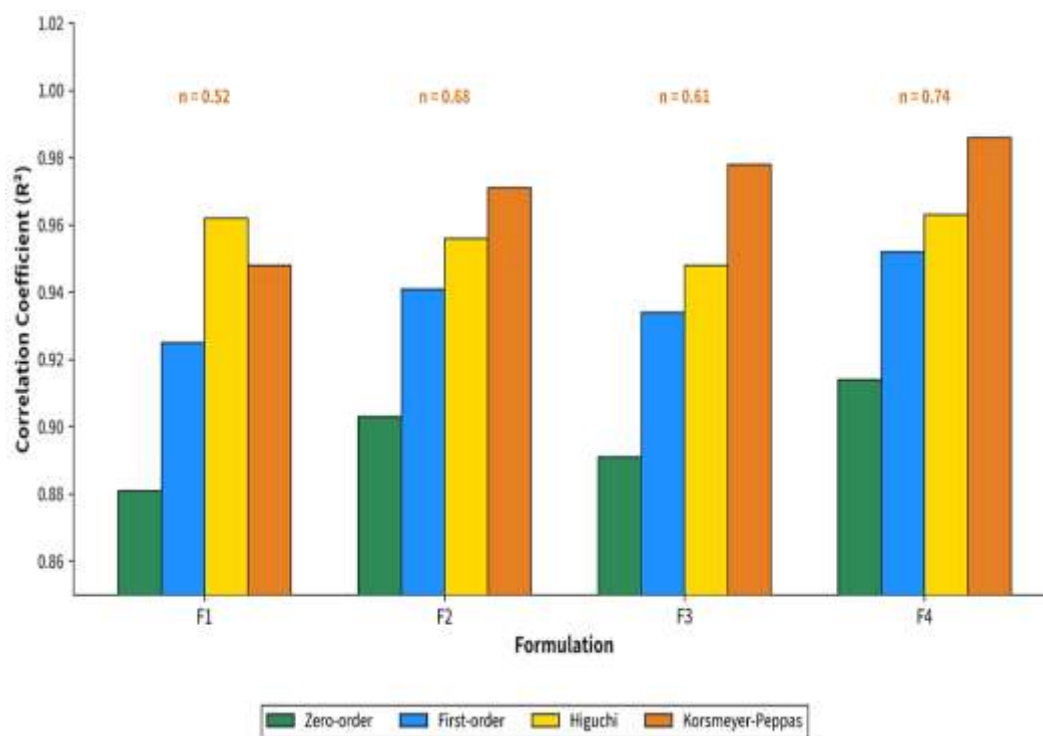


Fig. 5. Kinetic parameters obtained from fitting the DEX release data to different mathematical models.

3.7 | Stability of the Nanocomposite Formulations

The storage stability of the prepared formulations was evaluated over a period of 30 days at 4°C and 25°C by monitoring changes in particle size, PDI, zeta potential, and retained DEX content. The stability results for the drug-loaded formulations are summarized in Fig. 6. At 4°C, all formulations showed relatively limited changes in their physicochemical characteristics during the 30-day storage period. F4, which represented the final multifunctional nanocomposite, exhibited an initial particle size of 251.8 ± 9.1 nm, which increased slightly to 258.6 ± 9.5 nm after 30 days. The PDI increased from 0.26 ± 0.03 to 0.28 ± 0.03 , while the zeta potential changed from $+5.4 \pm 0.9$ mV to $+5.1 \pm 1.0$ mV. The retained DEX content after 30 days was $96.2 \pm 2.1\%$ of the initial value. At 25°C, a slightly greater change was observed. After 30 days, the particle size of F4 increased to 269.7 ± 10.4 nm, corresponding to an increase of approximately 7.1% relative to the initial value. The PDI increased to 0.31 ± 0.04 , while the zeta potential remained relatively stable at $+4.7 \pm 1.1$ mV. The retained DEX content was $92.8 \pm 2.5\%$, indicating that the majority of the incorporated drug remained associated with the nanocomposite during storage. F1 showed the smallest absolute particle size throughout the study but exhibited a somewhat greater relative increase at 25°C. In contrast, the polymer-coated formulations F2 and F4 maintained relatively stable particle-size distributions, particularly when stored at 4°C. This behavior suggests that the polymeric layers provided additional colloidal stabilization and reduced aggregation during storage. The changes in DEX content were also relatively limited at 4°C. After 30 days, the retained DEX contents of F1, F2, F3, and F4 were $93.8 \pm 2.3\%$, $95.1 \pm 2.0\%$, $94.6 \pm 2.2\%$, and $96.2 \pm 2.1\%$, respectively. At 25°C, the corresponding values decreased to $88.6 \pm 2.7\%$, $91.4 \pm 2.4\%$, $90.7 \pm 2.5\%$, and $92.8 \pm 2.5\%$. The final F4 formulation demonstrated satisfactory short-term storage stability, with only moderate changes in particle size and PDI and limited loss of incorporated DEX over 30 days. The greater stability observed at 4°C indicates that refrigerated storage is preferable for maintaining the physicochemical integrity and drug-retention capacity of the multifunctional nanocomposite.

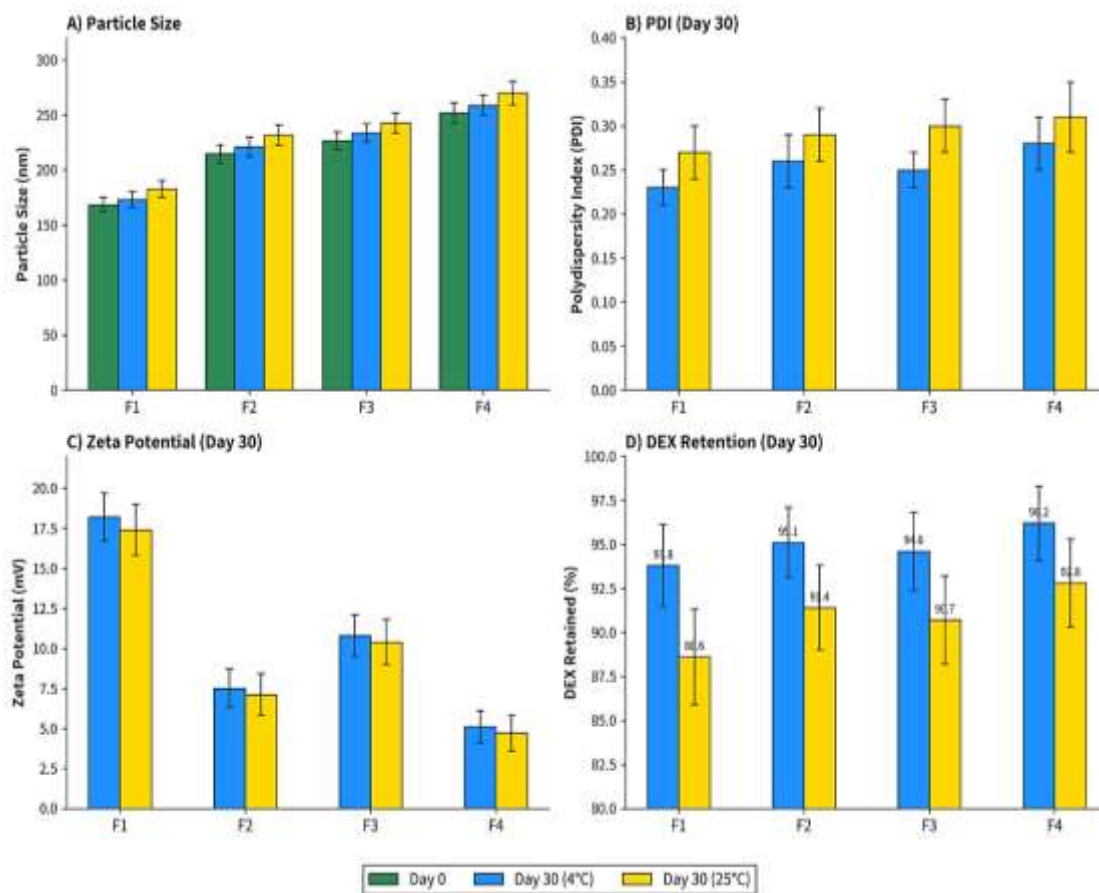


Fig. 6. Changes in physicochemical properties and DEX retention during 30-day storage.

3.8| In Vitro Cytocompatibility

The cytocompatibility of the prepared nanocomposite was evaluated using the MTT assay after exposure of cells to different concentrations of the blank carrier (F5) and the DEX-loaded multifunctional formulation (F4). Untreated cells were considered as the control group, and cell viability was expressed as a percentage of the untreated control. The results are presented in Fig. 7.

The blank nanocarrier F5 exhibited relatively high cytocompatibility over the investigated concentration range. At a concentration of 25 $\mu\text{g/mL}$, cell viability was $98.2 \pm 2.1\%$, while increasing the concentration to 50, 100, and 200 $\mu\text{g/mL}$ resulted in viabilities of $96.8 \pm 2.3\%$, $94.5 \pm 2.6\%$, and $91.7 \pm 2.8\%$, respectively. Even at the highest tested concentration, cell viability remained above 90%, indicating limited cytotoxicity associated with the carrier itself. The DEX-loaded F4 formulation showed a similar concentration-dependent pattern. Cell viability was $97.1 \pm 2.0\%$, $95.6 \pm 2.2\%$, $92.8 \pm 2.5\%$, and $89.6 \pm 2.9\%$ at 25, 50, 100, and 200 $\mu\text{g/mL}$, respectively. The slightly lower viability observed for F4 compared with F5 at the highest concentration may be associated with the biological activity of DEX and the higher overall cellular exposure to the drug-loaded nanocomposite.

At concentrations up to 100 $\mu\text{g/mL}$, both F4 and F5 maintained cell viability above 90%. No substantial reduction in viability was observed at these concentrations compared with the untreated control. These findings indicate that the multifunctional nanocomposite possesses an acceptable cytocompatibility profile within the concentration range selected for subsequent biological evaluation.

Importantly, the blank carrier did not produce a pronounced reduction in cell viability, suggesting that the CS/HA-PNIPAM-coated UiO-66-NH₂ architecture itself was relatively well tolerated under the experimental conditions. Therefore, the subsequent anti-inflammatory experiments were conducted using concentrations that maintained high cell viability while providing sufficient DEX exposure.

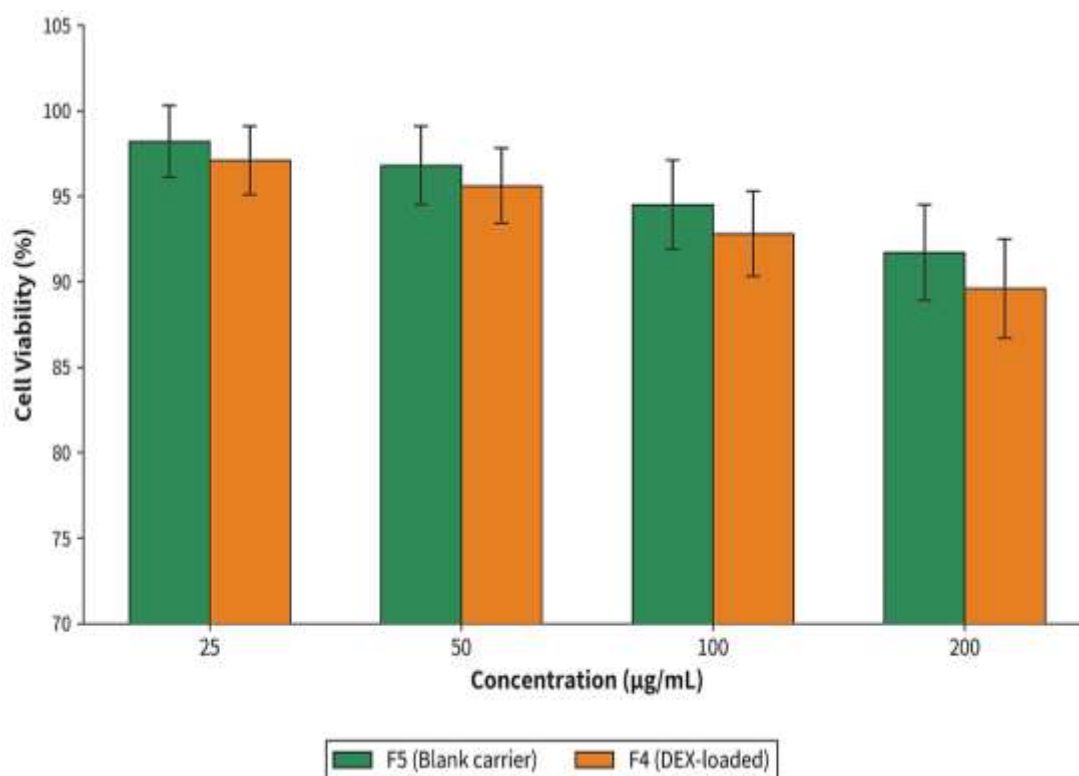


Fig. 7. Cell viability following exposure to F4 and F5 at different concentrations.

3.9| In Vitro Anti-Inflammatory Activity

The anti-inflammatory activity of the DEX-loaded multifunctional nanocomposite was evaluated using an LPS-stimulated cellular inflammation model. The levels of the pro-inflammatory cytokines TNF- α and IL-6 were measured following treatment with free DEX, the blank nanocarrier (F5), and the DEX-loaded multifunctional nanocomposite (F4). Untreated cells and LPS-stimulated cells were used as normal and inflammatory controls, respectively. The results are summarized in *Table 4*.

Exposure to LPS resulted in a pronounced increase in both inflammatory cytokines compared with untreated cells. The TNF- α concentration increased from 82.4 ± 6.3 pg/mL in untreated cells to 286.7 ± 14.8 pg/mL following LPS stimulation. Similarly, the IL-6 concentration increased from 54.6 ± 4.7 pg/mL to 238.5 ± 12.6 pg/mL, confirming successful induction of an inflammatory response. Treatment with free DEX reduced the concentrations of both cytokines. TNF- α decreased to 151.8 ± 9.7 pg/mL, while IL-6 decreased to 119.6 ± 8.4 pg/mL. These changes corresponded to reductions of approximately 47% and 50%, respectively, compared with the LPS-stimulated control. The blank nanocarrier F5 produced a comparatively limited effect on the inflammatory response. TNF- α and IL-6 concentrations were 258.4 ± 13.2 pg/mL and 213.7 ± 11.5 pg/mL, respectively. These values were only moderately lower than those observed in the LPS group, indicating that the CS/HA-PNIPAM-coated carrier itself did not account for the major anti-inflammatory response.

In contrast, treatment with F4 resulted in a more pronounced reduction in inflammatory cytokine production. TNF- α decreased to 108.6 ± 7.5 pg/mL, while IL-6 decreased to 82.3 ± 6.9 pg/mL. Compared with the LPS-stimulated control, F4 reduced TNF- α and IL-6 levels by approximately 62% and 65%, respectively. The lower cytokine concentrations observed after treatment with F4 compared with free DEX indicate that incorporation of DEX into the multifunctional nanocomposite was associated with a stronger suppression of the LPS-induced inflammatory response under the conditions tested. This behavior may be related to the sustained release of DEX from the UiO-66-NH₂ core and the ability of the CS/HA-PNIPAM coating to regulate drug diffusion. The relatively small effect observed for F5 further suggests that the reduction in inflammatory cytokines was primarily associated with the presence of DEX rather than an intrinsic anti-inflammatory effect of the blank carrier. The results demonstrate that the DEX-loaded multifunctional

nanocomposite effectively reduced LPS-induced production of TNF- α and IL-6 while maintaining acceptable cytocompatibility. The combination of controlled DEX release and the responsive polymeric architecture may therefore provide a useful strategy for sustained anti-inflammatory drug delivery.

Table 4. Effect of free DEX and nanocomposite formulations on LPS-induced inflammatory cytokine production.

Treatment Group	TNF- α (pg/mL)	IL-6 (pg/mL)
Untreated control	82.4 $\pm$ 6.3	54.6 $\pm$ 4.7
LPS	286.7 $\pm$ 14.8	238.5 $\pm$ 12.6
Free DEX	151.8 $\pm$ 9.7	119.6 $\pm$ 8.4
F5: Blank nanocarrier	258.4 $\pm$ 13.2	213.7 $\pm$ 11.5
F4: DEX-loaded nanocomposite	108.6 $\pm$ 7.5	82.3 $\pm$ 6.9

4 | Conclusion

In this study, a multifunctional DEX-loaded UiO-66-NH₂@CS/HA-PNIPAM nanocomposite was developed as a dual pH/temperature-responsive platform for controlled drug delivery and anti-inflammatory applications. Incorporating DEX into the porous UiO-66-NH₂ core, followed by sequential modification with CS/HA and PNIPAM, produced a nanoscale carrier with controlled surface properties, pH-dependent swelling, and temperature-responsive behavior [30].

Among the investigated formulations, the final F4 nanocomposite exhibited an EE% of 86.7 $\pm$ 2.0% and showed a more controlled DEX release compared with the uncoated UiO-66-NH₂ formulation. The combined polymeric architecture also produced pronounced changes in swelling and particle size in response to pH and temperature, indicating the contribution of CS/HA and PNIPAM to the stimuli-responsive behavior of the system. Release-kinetic analysis further suggested that DEX transport from the coated formulations was governed by a combination of diffusion and polymer-related hydration or relaxation mechanisms [27–30].

The biological evaluation demonstrated acceptable cytocompatibility of the final nanocomposite, with cell viability remaining above 90% at concentrations up to 100 μ g/mL. In the LPS-induced inflammatory model, F4 substantially reduced TNF- α and IL-6 concentrations compared with the inflammatory control, while the blank carrier produced only a limited effect. These findings indicate that the controlled delivery of DEX from the multifunctional nanocomposite can be associated with an enhanced anti-inflammatory response under the conditions investigated [22].

The results demonstrate that integrating a porous UiO-66-NH₂ drug-loading core with CS/HA and PNIPAM provides a practical strategy for combining high drug encapsulation, stimuli-responsive behavior, controlled release, and anti-inflammatory activity within a single nanocomposite platform. Further investigations, particularly long-term stability, detailed cellular mechanisms, and in vivo evaluation, are required to establish the therapeutic potential and translational applicability of this delivery system.

Authors' Contributions

All aspects of the research and manuscript preparation were carried out by the authors. The authors have read and approved the final version of the manuscript.

Data Availability

All data supporting the reported findings in this research paper are provided within the manuscript.

Funding

Not applicable.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

Consent for Publication

The authors confirm consent for the publication of this work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants performed by the authors.

References

- [1] Johnson, D. B., Lopez, M. J., & Kelley, B. (2023). *Dexamethasone*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK482130/>
- [2] Waldron, N. H., Jones, C. A., Gan, T. J., Allen, T. K., & Habib, A. (2013). Impact of perioperative dexamethasone on postoperative analgesia and side-effects: Systematic review and meta-analysis. *British Journal of Anaesthesia*, 110(2), 191–200. <https://doi.org/10.1093/bja/aes431>
- [3] Ahmed, M. H., & Hassan, A. (2020). Dexamethasone for the treatment of coronavirus disease (COVID-19): A review. *SN Comprehensive Clinical Medicine*, 2(12), 2637–2646. <https://doi.org/10.1007/s42399-020-00610-8>
- [4] Corcoran, T. B., Myles, P. S., Forbes, A. B., Cheng, A. C., Bach, L. A., O'Loughlin, E., ... & Ho, K. M. (2021). Dexamethasone and surgical-site infection. *New England Journal of Medicine*, 384(18), 1731–1741. <https://doi.org/10.1056/NEJMoa2028982>
- [5] Horby, P., Lim, W. S., Emberson, J., Mafham, M., Bell, J., Linsell, L., ... & Recovery Collaborative Group. (2020). Effect of dexamethasone in hospitalized patients with COVID-19—preliminary report. *MedRxiv*, 2020-06. <https://doi.org/10.1101/2020.06.22.20137273>
- [6] Baniasad, A., Baei, M. S., & Tala-Tapeh, S. M. (2025). Chitosan-PEGylated niosomes and liposomes as biomacromolecule carriers for Alzheimer's disease treatment: Galantamine drug delivery carrier. *Materials Chemistry and Physics*, 352, 132003. <https://doi.org/10.1016/j.matchemphys.2025.132003>
- [7] Niknejad, K., Sharifzadeh, B. M., & Motallebi, T. T. S. (2018). Synthesis of Metformin Hydrochloride nanoliposomes: Evaluation of physicochemical characteristics and release kinetics. *International Journal of Nano Dimension*, 9(3), 298–313. <https://www.sid.ir/paper/322408/en>
- [8] Divya, K., & Jisha, M. S. (2018). Chitosan nanoparticles preparation and applications. *Environmental Chemistry Letters*, 16(1), 101–112. <https://doi.org/10.1007/s10311-017-0670-y>
- [9] Mohammed, M. A., Syeda, J. T. M., Wasan, K. M., & Wasan, E. K. (2017). An overview of Chitosan nanoparticles and its application in non-parenteral drug delivery. *Pharmaceutics*, 9(4), 53. <https://doi.org/10.3390/pharmaceutics9040053>
- [10] Vashisth, V., Lakshmi, Dewangan, H. K., Sharma, N., & Jain, D. (2026). Smart delivery with Chitosan nanoparticles: Current innovations and future pathways. *Drug Delivery Letters*. <https://doi.org/10.2174/0122103031412053260112173343>
- [11] Jaaffer, M. D., Hadi, S. J., & Chaloo, A. M. (2026). Hyaluronic acid-targeted PLGA nanoparticles for methotrexate delivery in rheumatoid arthritis. *BioNatura Journal: Ibero-American Journal of Biotechnology and Life Sciences*, 3(2). <https://bionaturajournal.com/repositorio/index.php/bionatura/article/view/254>
- [12] Lin, C. W., Hu, W. P., & Su, W. Y. (2026). Hyaluronic acid nanoparticle as drug delivery carrier for the treatment of allergic conjunctivitis. *Bio-Medical Materials and Engineering*, 37(4-5), 241–252. <https://doi.org/10.1177/09592989261474686>
- [13] Du, X., Xu, S., Xu, F., Liu, Q., Wang, F., Deng, X., ... & Huang, P. (2026). Tumor-targeted delivery of curcumin via hyaluronic acid-functionalized polymeric nanoparticles: Characterization and mechanistic insights into PI3K/AKT/mTOR signaling. *BioNanoScience*, 16(8), 532. <https://doi.org/10.1007/s12668-026-02771-7>

- [14] Hasnawi, D. Al, Masheta, D., & Balakit, A. A. (2026). Rational design, development, and physicochemical characterization of gallic acid-and hyaluronic acid-functionalized selenium nanoparticles. *Journal of Nanostructures*, 16(4), 4605–4611. <https://doi.org/10.22052/JNS.2026.04.010>
- [15] Deng, Y. Z., Fu, K. L., Xie, R., Ju, X. J., Wang, W., Liu, Z., & Chu, L. Y. (2026). UCST-type thermo-responsive phase transition behavior of poly (N-isopropylacrylamide) in imidazolium-based ionic liquids. *Polymer*, 130330. <https://doi.org/10.1016/j.polymer.2026.130330>
- [16] Siddiqui, A., Touqeer, M., Ritu, F. A., Haider, M. A., Ahmed, A., James-Ocloo, O. S., ... & Huang, D. (2026). A review on thermoresponsive PNIPAM hydrogels for regenerative medicine: From mechanical design to tissue adhesion. *Regenerative Biomaterials*, 13, rbag045. <https://doi.org/10.1093/rb/rbag045>
- [17] Umar, A. K., Laomeephon, C., Pannarai, N., Lueantor, C., Thamnum, S., Kaewruethai, T., ... & Luckanagul, J. A. (2026). Mechanistic insights into the self-assembly and cellular uptake of thermoresponsive pNIPAM-grafted hyaluronic acid nanogels. *Journal of Pharmaceutical Investigation*, 56(5), 1067-1084. <https://doi.org/10.1007/s40005-025-00787-x>
- [18] Li, X., Bu, X., Huang, J., Li, Y., Wang, L., Miao, H., & Shi, G. (2026). A long-term stable thermochromic smart window of PNIPAM-based hydrogels with excellent water retention and visible light modulation. *Journal of Materials Chemistry A*, 14(18), 10657–10667. <https://doi.org/10.1039/d5ta09352j>
- [19] Qiang, X. Q., Wang, X., Du, C., Tang, Y., Wang, H., & Li, N. (2026). Thermoresponsive wettability-switchable PNIPAM composite fibers for enhanced moisture absorption and quick-drying in textiles. *Chemical Engineering Journal*, 178428. <https://doi.org/10.1016/j.cej.2026.178428>
- [20] Almazyad, A. F., Haq, N., Alsarra, I. A., Alshehri, S., Alam, P., Imran, M., & Shakeel, F. (2026). Novel drug delivery systems approved by USFDA from 2019 to 2023: A comprehensive review. *Current Drug Delivery*, 23(4), 396–422. <https://doi.org/10.2174/0115672018353367250317063449>
- [21] Hrapović, A., Islam, N., Al Bourghli, A., Sezer, A., Kovalenko, B., Lokvančić, H., ... & Uversky, V. N. (2026). Biomaterials in personalized drug delivery: Innovations, challenges, and future directions. *PeerJ*, 14, e20982. <https://doi.org/10.7717/peerj.20982>
- [22] Wei, X., Buse, J. B., Chen, H., Desai, T. A., Stevens, M. M., Traverso, G., ... & Gu, Z. (2026). Towards intelligent and miniaturized drug delivery devices. *Nature*, 651(8107), 897-908. <https://doi.org/10.1038/s41586-026-10221-3>
- [23] Adepu, S., & Ramakrishna, S. (2021). Controlled drug delivery systems: Current status and future directions. *Molecules*, 26(19), 5905. <https://doi.org/10.3390/molecules26195905>
- [24] Park, K. (2014). Controlled drug delivery systems: Past forward and future back. *Journal of Controlled Release*, 190, 3–8. <https://doi.org/10.1016/j.jconrel.2014.03.054>
- [25] Razzacki, S. Z., Thwar, P. K., Yang, M., Ugaz, V. M., & Burns, M. A. (2004). Integrated microsystems for controlled drug delivery. *Advanced Drug Delivery Reviews*, 56(2), 185–198. <https://doi.org/10.1016/j.addr.2003.08.012>
- [26] Yun, Y. H., Lee, B. K., & Park, K. (2015). Controlled drug delivery: Historical perspective for the next generation. *Journal of Controlled Release*, 219, 2–7. <https://doi.org/10.1016/j.jconrel.2015.10.005>
- [27] Nair, S., Ansari, A., Khan, S., Pratap, A., & Mali, S. N. (2026). Anti-inflammatory activity of silver nanoparticles (AgNPs): An updated systematic review from in vivo, and in vitro studies. *Inflammopharmacology*, 34(4), 2135–2174. <https://doi.org/10.1007/s10787-026-02167-9>
- [28] Hamed, A. M., Enaili, S. S., I. Mohammed, W., Abouelella, A. M., Mohana, Z. E. E., Monir, D. M., ... & El-Saghier, A. M. (2025). Novel benzenesulfonamide derivatives of 5'-aminospirotriazolotriazine exhibit anti-inflammatory activity by suppressing pro-inflammatory mediators: In vitro and in vivo evaluation using a rat model of carrageenan-induced paw edema. *Biomedicines*, 13(7), 1732. <https://doi.org/10.3390/biomedicines13071732>
- [29] Gago, C., Serralheiro, A., & Miguel, M. da G. (2025). Anti-inflammatory activity of thymol and thymol-rich essential oils: Mechanisms, applications, and recent findings. *Molecules*, 30(11), 2450. <https://doi.org/10.3390/molecules30112450>
- [30] Tan, X., Chen, P., Xiao, L., Gong, Z., Qin, X., Nie, J., ... & Zhong, S. (2025). Extraction, purification, structural characterization, and anti-inflammatory activity of a polysaccharide from *Lespedeza formosa*. *International Journal of Biological Macromolecules*, 300, 140154. <https://doi.org/10.1016/j.ijbiomac.2025.140154>