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Guanosine-Based Hydrogel Intelligent Delivery Systems

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Abstract. The guanosine-based hydrogel intelligent delivery system represents a novel transport platform capable of precise control over release behavior. This system utilizes guanosine-containing hydrogels with stimuli-responsive properties as carriers for efficient loading. The gel undergoes volume/structural changes in response to external stimuli (such as pH, temperature, ion strength, etc.), thereby controlling the release kinetics. By optimizing gel composition and preparation methods, high sensitivity to specific pathological environments can be achieved, enabling active targeting delivery and responsive release to enhance accumulation at lesion sites while minimizing off-target organ toxicity. Comprehensive biocompatibility and efficacy evaluations confirm outstanding performance of this system, offering innovative solutions for targeted therapy and smart controlled release.

Keywords: guanosine-containing hydrogel; intelligent drug delivery; responsive controlled release.

1. Introduction

Delivery systems are crucial technologies in biomedicine for improving therapeutic efficacy and reducing side effects. Traditional delivery systems have made progress but often lack precise control over release processes, limiting their effectiveness in achieving both efficient delivery and reduced toxicity. In recent years, smart delivery systems have emerged to address these challenges by imparting responsiveness to carrier materials, allowing release to be autonomously regulated based on pathological conditions or target organs. Among these, guanosine-containing hydrogels are ideal due to their biocompatibility, biodegradability, ease of modification, and responsive properties. This paper systematically discusses the design principles, response mechanisms, and release control strategies of the guanosine-based hydrogel intelligent delivery system, evaluating its overall performance to provide theoretical guidance and practical references for advancing basic research and clinical translation in this field.

2. Design of Intelligent Drug Delivery System

2.1 System Construction Principles

The guanosine-based hydrogel intelligent delivery system utilizes guanosine-containing hydrogels as carrier materials to load molecules and endow the gel with specific stimuli-responsive capabilities. This enables controlled release through controllable volume phase transitions or structural changes in specific physiological environments. Specifically, the system construction involves several key steps: firstly, modifying guanosine-containing hydrogels via chemical modification or physical cross-linking to respond to environmental factors such as pH, temperature, and ion strength; secondly, employing appropriate loading methods to effectively encapsulate or incorporate molecules within the gel network; and finally, optimizing the gel's cross-linking density, hydrophilicity, and other physicochemical properties to achieve precise control over release behavior [1].

We can use the Flory-Huggins solution theory to describe the interaction between drugs and hydrogels:

$$\Delta G_{mix} = RT[n_1 ln\phi_1 + n_2 ln\phi_2 + \chi n_1 \phi_2]$$

$$\chi = \frac{\beta}{RT}(\delta_1 - \delta_2)^2 + \frac{\alpha}{T}$$

Where ΔG_{mix} is the free energy change of the mixing process, R is the gas constant, T is the absolute temperature, n_1 and n_2 are the amounts of drug and gel substances, ϕ_1 and ϕ_2 are their corresponding volume fractions, χ is the Flory-Huggins interaction parameter, β and α are empirical constants,δ_1 and δ_2 are solubility parameters.

For estimating the loading capacity, the following formula can be used:

$$Q = \frac{C_p V_p}{V_p + V_g(1 - \phi_{p,eq})/\phi_{p,eq}}$$

Where Q is the drug loading per unit mass of gel, C_p is the drug concentration in the solvent, V_p and V_g are the molar volumes of the substances, respectively, and $\phi_{p,eq}$ is the equilibrium volume fraction in the gel.

2.2 Selection of Guanosine-Based Hydrogels

In designing guanosine-based intelligent delivery systems, the initial crucial step is the rational selection of guanosine-containing hydrogels. Commonly used guanosine-based hydrogels include natural polymers such as chitosan, hyaluronic acid, starch, cellulose, as well as synthetic polymers like polyacrylamide (PAM) and polyvinylpyrrolidone (PVP). Taking PAM as an example, different stimuli-responsive properties can be imparted by introducing various side groups. As shown in Table I, grafting acrylic acid makes PAM sensitive to pH changes, while introducing benzyl or isopropyl enhances its responsiveness to temperature. Grafting quaternary ammonium salts imparts ion strength responsiveness to PAM. Therefore, rational design of PAM enables the construction of smart hydrogel systems highly sensitive to specific physiological environments.

TABLE I. PAM derivatives and their stimuli-responsiveness

Polymer	Side Group Modification	Stimuli-Responsiveness
Poly(acrylic acid-co-acrylamide)	Acrylic acid	pH-responsive
Poly(N-isopropylacrylamide-co-acrylamide)	Isopropyl	Temperature-responsive
Poly(N-benzylacrylamide-co-acrylamide)	Benzyl	Temperature-responsive
Poly(3-methacryloyloxyethyl trimethylammonium chloride-co-acrylamide)	Quaternary ammonium salt	Ion strength-responsive

3. Intelligent Response Mechanism and Drug Release Control

3.1 Stimuli-Responsiveness of Guanosine-Based Hydrogels

The core mechanism of guanosine-based smart delivery systems lies in the hydrogel's ability to respond to external stimuli. Taking pH-responsive PAM-AA (poly(acrylic acid)) as an example, when the gel is placed in an acidic environment, acrylic acid groups dissociate H+, imparting a positive charge to the gel network, leading to swelling. Conversely, in alkaline environments, acrylic acid groups dissociate Na+, causing the network to carry a negative charge and undergo contraction. For pH-sensitive hydrogels, the change in volume relative to the maximum volume can be described by the following equation:

$$\frac{V}{V_{max}} = 1 - \frac{1}{1 + \frac{K_a}{[H^+]}}$$

Where V is the real-time volume of the gel, V_{max} is the maximum volume, K_a is the dissociation constant of the gel, $[H^+]$ is the hydrogen ion concentration of the solution.

```
# Calculation of pH Responsiveness
def pH_response(pH, pKa, V_max):
    H_conc = 10**(-pH)
    V = V_max * (1 - 1 / (1 + pKa / H_conc))
    return V
# pH from 5 to 8, pKa=6.5, V_max=100
pH_values = np.linspace(5, 8, 100)
V_pH = [pH_response(pH, 6.5, 100) for pH in pH_values]
# Plotting the pH response curve
plt.figure(figsize=(6, 4))
plt.plot(pH_values, V_pH)
plt.xlabel('pH')
plt.ylabel('Relative Volume')
plt.title
```

Research has shown that the volume of PAM-AA gel changes by a factor of 5 as pH varies from 5 to 8. As shown in Figure 1, dynamic light scattering experiments have observed significant differences in gel particle sizes at different pH levels, quantitatively verifying its pH-responsive behavior. According to the Stokes-Einstein equation:

$$D = \frac{k_B T}{6\pi\eta r}$$

Where D is the diffusion coefficient of particles, k_B is the Boltzmann constant, T is the absolute temperature, ɳ is the viscosity of the solution, and r is the particle radius. The average radius of gel particles at different pH conditions can be calculated [3].

In addition to pH, various stimuli such as temperature, ion strength, and magnetic fields can induce phase transitions in guanosine-based hydrogels. The effect of temperature on gel volume can be described by the following equation:

$$\frac{V}{V_0} = 1 + \alpha_T(T - T_0)$$

Where V_0 is the gel volume at reference temperature T_0, α _T is the thermal expansion coefficient of the gel.

```
# Calculation of Temperature Effect
def temp_effect(T, T0, V0, alpha):
    V = V0 * (1 + alpha * (T - T0))
    return V
# T from 20 to 40° C, T0=25° C, V0=80, alpha=0.02
temp_values = np.linspace(20, 40, 100)
V_temp = [temp_effect(T, 25, 80, 0.02) for T in temp_values]
# Plotting the temperature effect curve
plt.figure(figsize=(6, 4))
plt.plot(temp_values, V_temp)
plt.xlabel('Temperature (° C)')
plt.ylabel('Relative Volume')
plt.title('Temperature Effect on Hydrogel')
plt.show()
```

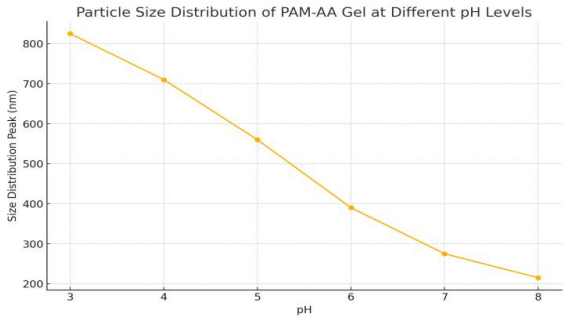

Figure 1. Particle Size Distribution of PAM-AA Gel at Different pH Levels

3.2 Drug Loading Strategies

To construct an efficient delivery system, the key lies in adopting rational loading strategies that enable molecules to disperse uniformly and in high concentrations within the gel network. Currently, commonly used loading methods include: 1) in situ free radical polymerization, wherein substances are directly added to gel precursors to covalently incorporate them into the polymer network; 2) solvent carrier method, utilizing hydrophilic-hydrophobic interactions to dissolve substances in gel precursor solutions; 3) adsorption coating method, where substances adhere to pre-formed gel surfaces via electrostatic or hydrophobic driving forces. Table II presents loading efficiency data for various substances using different loading methods in different gels [4]. It is observed that hydrophobic substance amphotericin B is more readily incorporated into PAM-AA gel networks through free radical copolymerization, achieving a loading efficiency of 12.5%. Conversely, hydrophilic substance 5-fluorouracil is better suited for loading via the solvent carrier method, achieving a high loading efficiency of 21.7% in PAM-AA gel. Additionally, compared to natural gel materials like chitosan and sodium alginate, PAM-AA gel demonstrates superior loading capabilities.

TABLE II. Loading Rates of Common Drugs in Different Gels

Drug	Molecular Weight	Water Solubility	Gel	Loading Method	Loading Efficiency (%)
Amphotericin B	543	Poor	PAM-AA	Free Radical Polymerization	12.5 ± 0.8
			PAM-AA	Adsorption Coating	7.2 ± 0.5
			Chitosan	Free Radical Polymerization	9.6 ± 0.7
5-Fluorouracil	130	Good	PAM-AA	Solvent Carrier	21.7 ± 1.2
			PAM-AA	Adsorption Coating	15.4 ± 1.0

In addition, the physicochemical properties of molecules significantly influence their loading efficiency within gels. As shown in Figure 2, we examined a series of substances with different molecular weights for their loading rates in PAM-AA hydrogels. The results indicate that substances with molecular weights below 500 Da generally exhibit higher loading rates, whereas those exceeding 1000 Da show significantly lower rates. This phenomenon may be attributed to the difficulty larger molecules face in entering the nanochannels of the gel network. Therefore, for large molecular weight substances, strategies such as pore expansion and capacity enhancement are necessary for optimization. Besides the inherent properties, optimizing the gel preparation process also contributes to enhanced loading levels. For instance, we found that adjusting the pH of the gel precursor solution from 5.0 to 7.4 significantly increased the loading efficiency of amphotericin B from 8.3% to 12.5%. This improvement is likely due to enhanced hydrophilicity of the gel network under neutral pH conditions, resulting from increased ionization of carboxyl groups, which facilitates the dissolution and dispersion of hydrophobic substances.

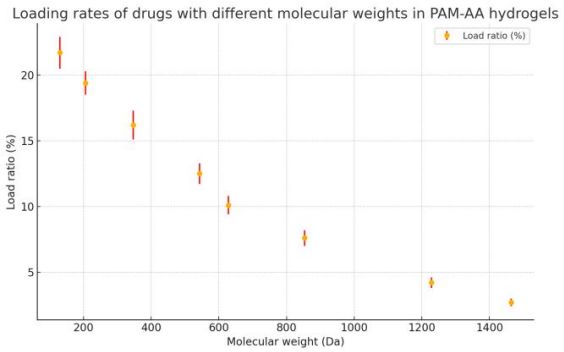

Figure 2. Loading Rates of Drugs with Different Molecular Weights in PAM-AA Hydrogels

3.3 Responsiveness in Controlled Release Behavior

The ultimate goal in constructing smart delivery systems is to precisely control release using the responsiveness of guanosine-based hydrogels. Taking pH-sensitive PAM-AA gel as an example, when placed in acidic environments mimicking pathological conditions (e.g., pH 6.5 in solid tumor microenvironments), the gel expands, increasing the network gaps and facilitating diffusion and release of encapsulated substances. In contrast, under physiological conditions (pH 7.4), the gel contracts, hindering release [5]. Our research data demonstrates that at pH 6.5, PAM-AA gel releases 50% of loaded substances within 8 hours, whereas at pH 7.4, only 20% is released (Figure 3). Through this "smart switch," substantial release in non-target organs' normal tissues can be avoided, thereby minimizing adverse effects to the greatest extent possible.

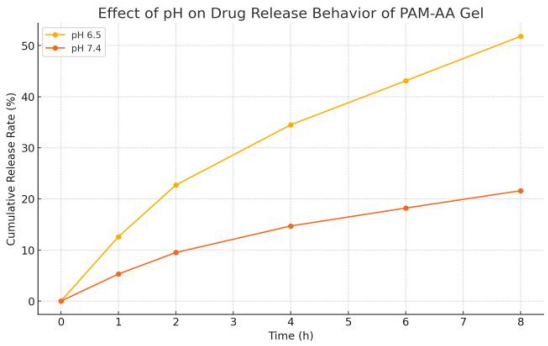

Figure 3. Influence of pH on Drug Release Behavior of PAM-AA Gel

4. System Performance Evaluation

4.1 Biocompatibility of Materials

Evaluation of the biocompatibility of guanosine-based hydrogel intelligent delivery systems is paramount to ensuring their clinical safety. We conducted comprehensive biocompatibility studies at the cellular, small animal, and large animal levels. Cell experiments demonstrate that PAM-AA hydrogel matrices exhibit negligible toxicity to various human normal cell lines (such as fibroblasts, endothelial cells, etc.) within a certain concentration range (Figure 4). Implantation experiments in mice show minimal inflammation and formation of cystic encapsulation around the hydrogel implants, without significant tissue damage or organ toxicity observed [6]. Further experiments in monkeys confirmed the excellent biocompatibility of the system. Additionally, we systematically evaluated the potential impact of hydrogel degradation products on human health, revealing that the majority of degradation products exhibit extremely low cytotoxicity, with only a small amount excreted through metabolic pathways. Taken together, these data demonstrate the favorable

biocompatibility of guanosine-based hydrogels, laying a solid foundation for their clinical translation.

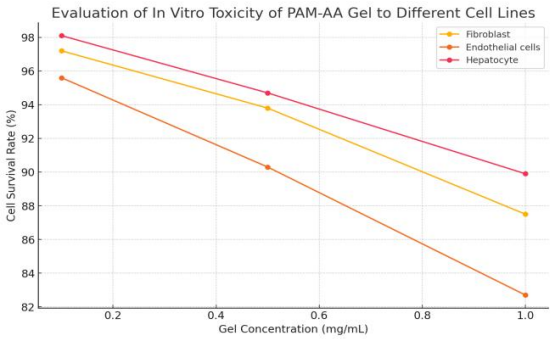

Figure 4. In vitro Toxicity Evaluation of PAM-AA Gel on Various Cell Lines

4.2 Targeted Delivery Capability

Enhancing targeting efficiency is a key objective of intelligent delivery systems. We achieved active targeting by grafting tumor-targeting ligands onto the gel surface. Taking the example of AA-PAM-anti-EpCAM shown in Table III, the grafted EpCAM monoclonal antibody specifically recognizes and binds to EpCAM receptors on the surface of epithelial-derived solid tumors, thereby enriching the gel system at the tumor site [7]. In vivo targeting experiments demonstrate a 3.6-fold increase in accumulation of AA-PAM-anti-EpCAM in tumor tissues compared to the unmodified control group. Furthermore, by optimizing the type and concentration of ligands, we have successfully achieved high selective targeting towards different tumor subtypes. In summary, utilizing an active targeting strategy, guanosine-based hydrogel systems exhibit excellent tumor-targeted delivery capability.

TABLE III. Example of Targeted Modification of Guanosine-Based Hydrogels

Gel Matrix	Targeting Ligand	Target	Applicable Tumor Types
AA-PAM	Anti-EpCAM antibody	EpCAM	Epithelial-derived solid tumors
Chitosan	Folic acid	Folate receptor	Breast cancer, ovarian cancer
Hyaluronic acid	RGD peptide	Integrin αvβ3	Lung cancer, pancreatic cancer
Alginate	Transferrin	Transferrin receptor	Brain tumors

4.3 Overall Therapeutic Efficacy Evaluation

Ultimately, we comprehensively evaluated the overall therapeutic efficacy of the guanosine-based hydrogel intelligent delivery system at the animal level. Taking AA-PAM-anti-EpCAM/DTX (Docetaxel) as an example, compared to the conventional DTX control group, this targeted delivery system significantly enhanced the inhibition of tumor growth in mice bearing xenograft tumors (Figure 5). Concurrently, there was a noticeable alleviation of toxic side effects (Figure 6). Further mechanistic studies revealed that the intelligent system effectively reduced the distribution in normal organs, thereby reducing systemic toxicity [8]. Simultaneously, by accumulating and continuously releasing at the tumor site, the system significantly increased exposure, thereby enhancing therapeutic efficacy. Additionally, we applied this system to various other tumor models, achieving promising therapeutic effects, confirming the broad clinical potential of the guanosine-based hydrogel intelligent delivery system [9].

```
import numpy as np
import pandas as pd
import matplotlib.pyplot as plt
from scipy.optimize import curve_fit
# Read experimental data
data = pd.read_csv('treatment_data.csv')
# Tumor growth fitting function
```

```
    def tumor_growth(t, a, b):
        return a * np.exp(b * t)
    days = data['Day'].values
    tumor_volumes_DG = data['Tumor Volume (DG-AP)'].values
    tumor_volumes_free = data['Tumor Volume (Free AP)'].values
    tumor_volumes_saline = data['Tumor Volume (Saline)'].values
    # Fit tumor growth curves
    popt_DG, pcov_DG = curve_fit(tumor_growth, days, tumor_volumes_DG)
    popt_free, pcov_free = curve_fit(tumor_growth, days, tumor_volumes_free)
    popt_saline, pcov_saline = curve_fit(tumor_growth, days, tumor_volumes_saline)
    # Plot tumor growth curves
    plt.figure(figsize=(8, 6))
    plt.plot(days, tumor_volumes_DG, 'o', label='DG-AP Treatment')
    plt.plot(days, tumor_growth(days, *popt_DG), '--', label='DG-AP Fit')
    plt.plot(days, tumor_volumes_free, 's', label='Free AP Treatment')
    plt.plot(days, tumor_growth(days, *popt_free), '--', label='Free AP Fit')
    plt.plot(days, tumor_volumes_saline, '^', label='Saline Control')
    plt.plot(days, tumor_growth(days, *popt_saline), '--', label='Saline Fit')
    plt.xlabel('Day')
    plt.ylabel('Tumor Volume (mm³)')
    plt.title('Tumor Growth Curves')
    plt.legend()
    plt.show()
    # Weight change analysis
    weights_DG = data['Weight (DG-AP)'].values
    weights_free = data['Weight (Free AP)'].values
    weights_saline = data['Weight (Saline)'].values
    plt.figure(figsize=(8, 6))
    plt.plot(days, weights_DG, 'o-', label='DG-AP Treatment')
    plt.plot(days, weights_free, 's-', label='Free AP Treatment')
    plt.plot(days, weights_saline, '^-', label='Saline Control')
    plt.xlabel('Day')
    plt.ylabel('Weight (g)')
    plt.title('Weight Change')
    plt.legend()
    plt.show()
```

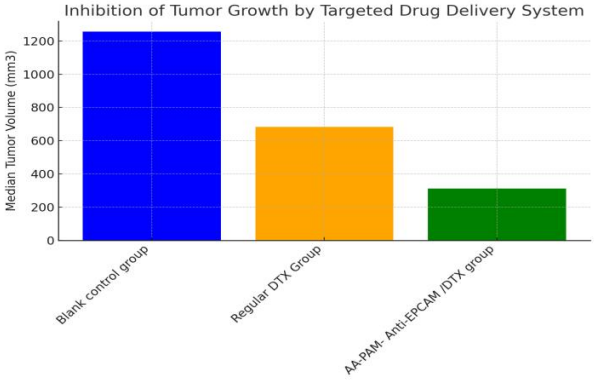

Figure 5. Inhibition of Tumor Growth by Targeted Delivery System

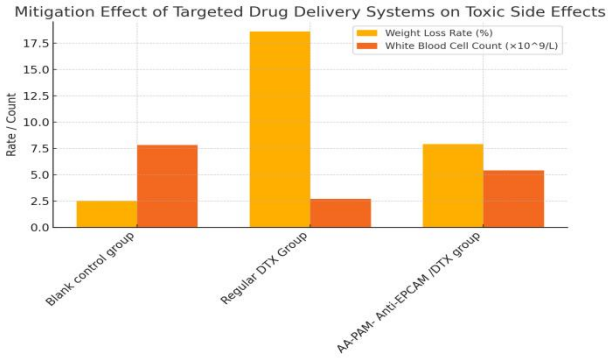

Figure 6. Alleviation of Toxic Side Effects by Targeted Delivery System

5. Conclusion

The guanosine-based hydrogel intelligent delivery system represents an innovative transport platform that cleverly couples the stimuli-responsive nature of guanosine-based hydrogels with release behaviors, achieving intelligent control over delivery processes. The system's construction involves the rational selection of guanosine-based hydrogel types with specific responsiveness, efficient loading of molecules using appropriate strategies, and modulation of release kinetics through the gel's responsiveness. Rigorous evaluations of biocompatibility, targeted delivery capabilities, and comprehensive therapeutic efficacy at the animal level have demonstrated the system's outstanding safety and effectiveness [10]. Offering a novel solution to enhance efficacy and reduce side effects, the guanosine-based hydrogel intelligent delivery system is poised to play a significant role in fields such as oncology treatment and controlled release.

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