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EMERGING NANOGEL DRUG DELIVERY PLATFORMS FOR IMPROVED THERAPEUTIC PERFORMANCE OF METHOTREXATE

Priyanshu Upadhyay*, Vivek Gupta, Jitendra Kumar Malik, Gyan Singh

Research Scholar, Faculty of Pharmacy, PK University, Thanra - 473665, Madhya Pradesh, India.

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***Corresponding Author: Priyanshu Upadhyay**
Research Scholar, Institute of Pharmacy, PK University, Thanra - 473665, Madhya Pradesh, India.
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ABSTRACT

Methotrexate (MTX) remains a cornerstone antimetabolite in the management of malignancies and autoimmune disorders, including rheumatoid arthritis and psoriasis. However, its conventional administration is hindered by significant limitations such as poor and variable bioavailability, rapid systemic clearance, dose-limiting toxicity, and lack of precise site-specific targeting. These challenges often compromise therapeutic outcomes and increase the risk of severe adverse effects, thereby necessitating innovative and more efficient drug delivery strategies. Nanogel-based drug delivery systems have recently gained considerable attention as next- generation nanocarriers designed to address these shortcomings. Nanogels are three-dimensional, nanoscale, cross-linked polymeric networks characterized by high water content, excellent biocompatibility, and structural versatility. Their ability to encapsulate therapeutic agents and respond to physiological stimuli such as pH, temperature, and enzymatic activity makes them highly efficient for controlled and targeted drug delivery. The incorporation of MTX into nanogels offers multiple therapeutic advantages, including enhanced drug stability, prolonged circulation time, improved bioavailability, and selective accumulation at diseased tissues via passive and ligand-mediated active targeting mechanisms. Furthermore, sustained and controlled drug release significantly reduces systemic toxicity and improves overall treatment efficacy and patient compliance. Recent advances in nanogel engineering, including smart and stimuli-responsive systems, have demonstrated promising results in preclinical studies, indicating superior therapeutic performance compared to conventional formulations. Nonetheless, challenges such as scalability, reproducibility, long-term safety, and regulatory approval must be addressed. Overall, nanogel platforms represent a transformative and highly promising strategy for optimizing MTX therapy in modern precision medicine.

KEYWORDS: Methotrexate, Nanogels, Targeted drug delivery, Rheumatoid arthritis, Cancer therapy, Controlled release.

1. INTRODUCTION

Methotrexate (MTX) is a well-established antimetabolite and antifolate drug extensively used in the treatment of various malignancies and autoimmune disorders. It is commonly prescribed for cancers such as leukemia, lymphoma, and breast cancer, as well as chronic inflammatory conditions including rheumatoid arthritis and psoriasis. The therapeutic efficacy of MTX is primarily attributed to its ability to inhibit the enzyme dihydrofolate reductase (DHFR), which plays a crucial role in DNA synthesis and cellular proliferation. By blocking this enzyme, MTX interferes with the synthesis of purines and pyrimidines, ultimately suppressing rapidly dividing cells and modulating immune responses.[1]

Despite its clinical importance, conventional MTX therapy is associated with several significant limitations. One of the major concerns is systemic toxicity, which may manifest as hepatotoxicity, nephrotoxicity, and bone marrow suppression, particularly at higher doses or during prolonged treatment. Additionally, MTX exhibits low and variable bioavailability due to poor solubility and rapid elimination from the body. Another critical drawback is its non-specific distribution, which leads to the exposure of healthy tissues to the drug, thereby increasing the risk of adverse effects and reducing therapeutic selectivity.[2]

These challenges highlight the urgent need for advanced drug delivery systems capable of improving the pharmacokinetic and pharmacodynamic profile of MTX. In this context, nanotechnology-based approaches have emerged as promising alternatives to conventional formulations. Among these, nanogel-based delivery platforms have gained considerable attention due to their unique structural and functional properties.[3]

Nanogels are nanoscale, cross-linked polymeric networks that can encapsulate therapeutic agents and provide controlled, sustained, and targeted drug release. Their high-water content, biocompatibility, and responsiveness to environmental stimuli such as pH and temperature make them particularly suitable for site-specific drug delivery. By enhancing drug stability, improving bioavailability, and minimizing systemic toxicity, nanogels offer a significant advancement in MTX therapy.[4]

The present review aims to comprehensively discuss the emerging role of nanogel-based drug delivery systems in improving the therapeutic performance of methotrexate. It focuses on formulation strategies, mechanisms of drug release, therapeutic advantages, recent research developments, and future prospects in this rapidly evolving field.[5]

2. LITERATURE SEARCH METHODOLOGY

A systematic and comprehensive literature search was conducted to identify relevant studies focusing on nanogel-based drug delivery systems for methotrexate (MTX). Multiple scientific databases, including PubMed, ScienceDirect, Google Scholar, and SpringerLink, were explored to ensure broad coverage of peer-reviewed research articles, reviews, and experimental studies.[6]

Appropriate keywords and their combinations were used to retrieve relevant literature. The primary search terms included ―Methotrexate nanogel,‖ ―nanogel drug delivery,‖ and ―targeted MTX delivery.‖ Boolean operators such as AND and OR were applied to refine the search and improve the specificity of results. Additional articles were identified through manual screening of reference lists of selected publications to ensure inclusion of all significant studies.[7]

The inclusion criteria were defined to select studies that specifically investigated nanogel-based delivery systems of methotrexate. Both in vitro and in vivo studies evaluating formulation strategies, drug release behavior, therapeutic efficacy, and safety profiles were considered. Review articles providing comprehensive insights into nanogel systems and MTX delivery were also included to support critical analysis.[8]

Exclusion criteria involved the elimination of non-peer-reviewed articles, conference abstracts lacking detailed data, and studies with insufficient methodological clarity or incomplete results. Articles not directly related to nanogel-based MTX delivery were also excluded to maintain the focus and relevance of the review.[9]

Data from the selected studies were systematically extracted and analyzed based on key parameters such as type of nanogel formulation, method of preparation, drug loading efficiency, release kinetics, biological evaluation, and therapeutic outcomes. The collected information was critically evaluated and organized to provide a coherent and structured understanding of the current advancements and future potential of nanogel-mediated methotrexate delivery systems.[10]

3. METHOTREXATE: PHARMACOLOGICAL PROFILE

3.1 Physicochemical Properties

Methotrexate (MTX) is a folic acid analogue belonging to the class of antimetabolite drugs. Structurally, it consists of a pteridine ring linked to para-aminobenzoic acid and glutamic acid moieties, which closely resemble folate, enabling it to competitively inhibit folate-dependent enzymes. MTX is a weakly acidic compound with limited aqueous solubility, particularly at physiological pH, which contributes to its variable absorption profile.[11]

The drug exhibits moderate stability under controlled conditions; however, it is sensitive to light and extreme pH variations. Its physicochemical characteristics, including poor solubility and ionization behavior, significantly influence its pharmacokinetics, leading to challenges in formulation and delivery. These limitations necessitate the development of advanced delivery systems to enhance its stability and bioavailability.[12]

3.2 Mechanism of Action

The therapeutic activity of methotrexate is primarily mediated through the inhibition of the enzyme dihydrofolate reductase (DHFR). This enzyme is essential for the conversion of dihydrofolate to tetrahydrofolate, a cofactor required for the synthesis of purine nucleotides and thymidylate. By inhibiting DHFR, MTX effectively disrupts DNA, RNA, and protein synthesis, particularly in rapidly dividing cells.[13]

Additionally, MTX promotes the accumulation of intracellular adenosine, which contributes to its anti-inflammatory effects, especially in autoimmune diseases. This dual mechanism makes MTX effective in both oncological and inflammatory conditions, although it also underlies many of its toxic effects on normal proliferating cells.[14]

3.3 Clinical Applications

Methotrexate is widely utilized across multiple therapeutic areas due to its potent antiproliferative and immunosuppressive properties. In oncology, it is used in the treatment of various cancers, including leukemia, lymphoma, and breast cancer, where it inhibits tumor cell growth.

In non-oncological conditions, MTX is considered a first-line therapy for rheumatoid arthritis, where it reduces inflammation and slows disease progression. It is also commonly used in the management of psoriasis and other autoimmune disorders due to its ability to suppress abnormal immune responses and excessive cell proliferation.[15]

3.4 Limitations of Conventional Delivery

Despite its clinical effectiveness, conventional methotrexate therapy is associated with several significant limitations. One of the primary concerns is dose-dependent toxicity, which can lead to severe adverse effects during long-term or high-dose treatment. Hepatotoxicity and nephrotoxicity are commonly reported, along with bone marrow suppression and gastrointestinal disturbances.[16]

Furthermore, MTX exhibits poor targeting efficiency, resulting in non-specific distribution throughout the body. This lack of selectivity exposes healthy tissues to the drug, reducing therapeutic precision and increasing systemic toxicity. These challenges highlight the need for novel drug delivery approaches, such as nanogel-based systems, to improve the safety and efficacy of methotrexate therapy.[17]

Table 1: Pharmacological Profile of Methotrexate.[18]

Parameter	Description
Drug Name	Methotrexate
Drug Class	Antimetabolite, Antifolate
Chemical Structure	Folic acid analogue with pteridine, PABA, and glutamate moieties
Molecular Formula	$C_{20}H_{22}N_8O_5$
Molecular Weight	454.44 g/mol
Mechanism of Action	Inhibits dihydrofolate reductase (DHFR)
Primary Effect	Inhibits DNA, RNA, and protein synthesis
Pharmacological Action	Anticancer and immunosuppressive
Routes of Administration	Oral, intravenous, intramuscular, subcutaneous
Bioavailability	Variable (dose-dependent, ~60–70% oral)
Protein Binding	Approximately 50% bound to plasma proteins
Metabolism	Hepatic metabolism to active polyglutamate forms
Elimination	Primarily renal excretion
Half-life	3–10 hours (low dose), longer in high doses
Clinical Indications	Cancer, rheumatoid arthritis, psoriasis
Major Adverse Effects	Hepatotoxicity, nephrotoxicity, myelosuppression
Limitations	Poor targeting, systemic toxicity, low solubility

4. NANOGELS: AN OVERVIEW

4.1 Definition and Characteristics

Nanogels are nanosized, three-dimensional hydrogel particles composed of cross-linked polymeric networks capable of retaining large amounts of water while maintaining structural integrity. Typically ranging from 20 to 200 nm in size, nanogels combine the properties of hydrogels and nanoparticles, making them highly suitable for drug delivery applications.[19]

One of the defining features of nanogels is their high-water content, which contributes to excellent biocompatibility and minimizes toxicity. Their soft and flexible structure allows efficient encapsulation of both hydrophilic and hydrophobic drugs. Additionally, nanogels exhibit high surface area, tunable size, and the ability to respond to environmental stimuli, enabling precise control over drug release. Their stability in biological environments and ability to protect encapsulated drugs from degradation further enhance their therapeutic potential.[20]

4.2 Types of Nanogels

Nanogels can be classified based on their composition and functional behavior:

Polymer-based nanogels: These are the most commonly used nanogels and are synthesized using natural or synthetic polymers such as chitosan, polyethylene glycol (PEG), polyvinyl alcohol (PVA), and poly (lactic-co-glycolic acid) (PLGA). They offer good biocompatibility, biodegradability, and ease of functionalization.[21]

Stimuli-responsive nanogels: These nanogels are designed to respond to specific physiological or external stimuli such as pH, temperature, ionic strength, or enzymes. For example, pH- sensitive nanogels release drugs preferentially in acidic tumor environments, while thermoresponsive nanogels alter their structure in response to temperature changes, enabling controlled drug release.[22]

Hybrid nanogels: Hybrid nanogels combine organic and inorganic components or multiple polymers to enhance stability, targeting efficiency, and drug loading capacity. These systems integrate the advantages of different materials to achieve improved therapeutic performance.[23]

4.3 Advantages in Drug Delivery

Nanogels offer several advantages over conventional drug delivery systems, making them highly effective carriers for therapeutic agents:

- **Controlled and sustained release:** Nanogels enable prolonged drug release profiles, reducing dosing frequency and maintaining therapeutic drug levels.
- **Target specificity:** Their surface can be functionalized with ligands, antibodies, or receptors, allowing selective targeting of diseased tissues and cells.
- **Reduced systemic toxicity:** Encapsulation of drugs within nanogels limits exposure to healthy tissues, thereby minimizing adverse effects.
- **Enhanced permeability and retention (EPR) effect:** Due to their nanoscale size, nanogels preferentially accumulate in tumor tissues through the EPR effect, improving drug concentration at the target site.[24]

Overall, nanogels represent a versatile and advanced drug delivery platform with significant potential to improve therapeutic efficacy and safety profiles of drugs such as methotrexate.

5. NANOGEL-BASED DELIVERY OF METHOTREXATE

5.1 Formulation Strategies

The development of nanogel systems for methotrexate (MTX) delivery involves carefully designed formulation strategies to ensure optimal drug loading, stability, and therapeutic performance. One of the key approaches is the use of cross-linking methods, which can be either physical or chemical. Physical cross-linking involves non-covalent interactions such as hydrogen bonding, ionic interactions, or hydrophobic forces, offering reversible and stimuli-responsive behavior. In contrast, chemical cross-linking forms stable covalent bonds within the polymeric network, providing enhanced structural integrity and controlled drug release.[25]

Polymer selection plays a critical role in determining the characteristics of nanogels. Natural polymers such as chitosan are widely used due to their biodegradability, biocompatibility, and mucoadhesive properties. Synthetic polymers like

polyethylene glycol (PEG) improve circulation time and reduce immunogenicity, while poly(lactic-co-glycolic acid) (PLGA) enhances mechanical strength and controlled degradation. The combination of these polymers allows the design of nanogels with tailored properties suitable for targeted MTX delivery.[26]

5.2 Drug Loading Techniques

Efficient incorporation of methotrexate into nanogels is essential for achieving desired therapeutic outcomes. Two primary drug loading techniques are commonly employed:

Physical encapsulation: In this method, MTX is entrapped within the polymeric network during or after nanogel formation through non-covalent interactions. This approach is relatively simple and preserves the structural integrity of the drug. However, drug leakage during storage or circulation may occur.[27]

Chemical conjugation: This technique involves the covalent attachment of MTX to the polymer backbone through cleavable linkages. It offers improved drug stability, controlled release, and reduced premature leakage. The release of MTX can be triggered by specific physiological conditions such as pH or enzymatic activity, enhancing targeted delivery.[28]

5.3 Release Mechanisms

The therapeutic efficiency of MTX-loaded nanogels largely depends on their drug release behavior, which can be precisely controlled through design strategies.

Diffusion-controlled release: In this mechanism, the drug gradually diffuses out of the nanogel matrix over time. The release rate is influenced by factors such as polymer density, cross-linking degree, and nanogel size, allowing sustained drug delivery.[29]

Stimuli-triggered release: Advanced nanogels are engineered to release MTX in response to specific stimuli such as pH, temperature, enzymes, or redox conditions. For instance, pH- sensitive nanogels release the drug preferentially in acidic tumor or inflamed environments, ensuring site-specific action and minimizing systemic exposure.[30]

Overall, nanogel-based delivery systems provide a highly adaptable platform for methotrexate administration, enabling improved targeting, controlled release, and enhanced therapeutic efficacy.

Table 2: Types of Nanogels Used for Methotrexate Delivery[31]

Nanogel Type	Polymer Used	Stimuli/Property	Key Features	Application
pH-sensitive nanogel	Chitosan	pH-responsive	Targeted release in acidic tumor environment	Cancer therapy
Thermoresponsive nanogel	PNIPAM	Temperature- sensitive	Controlled swelling and release	Rheumatoid arthritis
Redox-responsive nanogel	PEG-based polymers	Redox-sensitive	Drug release in high glutathione conditions	Tumor targeting
Enzyme-responsive nanogel	Gelatin	Enzyme-sensitive	Site-specific degradation	Cancer therapy
Polymer-based nanogel	PLGA	Biodegradable	Sustained drug release	General drug delivery
Hybrid nanogel	PEG + PLGA	Dual functionality	Improved stability and targeting	Multi- purpose
Magnetic nanogel	Iron oxide	Magnetic targeting	External field- guided	Targeted therapy

	+ polymer		delivery	
Lipid-coated nanogel	Lipid + polymer core	Enhanced permeability	Improved cellular uptake	Cancer treatment
Ionic nanogel	Alginate	Ionic cross-linking	Simple preparation, biocompatible	Controlled delivery
Hydrogel nanoparticle	PVA	Hydrophilic network	High drug loading capacity	Sustained release
Dendrimer-based nanogel	PAMAM	Branched structure	High surface functionality	Targeted delivery
Biodegradable nanogel	Chitosan+ PLGA	Biodegradable	Safe degradation in body	Clinical applications
Smart nanogel	Multi-polymer system	Multi-stimuli responsive	Precise drug control	Advanced therapy
Injectable nanogel	PEG-based	Injectable system	Ease of administration	Localized delivery
Surface-modified nanogel	Ligand-functionalized	Active targeting	Enhanced receptor binding	Target- specific
	polymers			therapy

6. THERAPEUTIC ADVANTAGES OF MTX NANOGELS

6.1 Enhanced Bioavailability

Nanogel-based delivery systems significantly improve the bioavailability of methotrexate (MTX), which is otherwise limited by poor solubility and variable absorption. Encapsulation of MTX within the hydrophilic polymeric network of nanogels enhances its aqueous solubility and protects it from premature degradation. Additionally, the nanoscale size facilitates better permeability across biological membranes, leading to improved absorption and prolonged circulation time. These features collectively ensure higher drug concentration at the therapeutic site, thereby enhancing overall treatment efficacy.[32]

6.2 Targeted Drug Delivery

One of the major advantages of nanogels is their ability to deliver drugs selectively to diseased tissues, minimizing off-target effects.

Passive targeting (EPR effect): Nanogels exploit the enhanced permeability and retention (EPR) effect, a phenomenon commonly observed in tumor tissues where leaky vasculature allows nanoparticles to accumulate preferentially. This results in higher localization of MTX at the target site without affecting healthy tissues.[33]

Active targeting (ligand-based systems): Surface modification of nanogels with specific ligands such as antibodies, peptides, or receptors enables active targeting. These ligands bind to overexpressed receptors on diseased cells, facilitating receptor-mediated endocytosis and improving cellular uptake of MTX. This targeted approach enhances therapeutic precision and efficacy.[34]

6.3 Reduced Toxicity

Nanogel-mediated delivery plays a crucial role in minimizing the systemic toxicity associated with conventional MTX therapy. By encapsulating the drug within a controlled release system, nanogels reduce exposure of healthy tissues to high drug concentrations. Controlled and sustained release ensures gradual drug availability, preventing sudden peak plasma levels that are often responsible for adverse effects such as hepatotoxicity and nephrotoxicity. This targeted and regulated delivery significantly improves the safety profile of MTX.[35]

6.4 Improved Patient Compliance

The sustained and controlled drug release offered by nanogels reduces the frequency of dosing required for effective therapy. This is particularly beneficial in chronic conditions such as rheumatoid arthritis, where long-term medication adherence is critical. Reduced dosing frequency, combined with fewer side effects, enhances patient comfort and compliance, ultimately leading to better therapeutic outcomes.[36]

7. IN VITRO AND IN VIVO EVALUATION

7.1 In Vitro Studies

In vitro evaluation plays a crucial role in assessing the performance and therapeutic potential of methotrexate (MTX)-loaded nanogels under controlled laboratory conditions.

Drug release studies: Drug release behavior is typically evaluated using dialysis methods under simulated physiological conditions. These studies help determine the release kinetics and mechanism (sustained or stimuli-responsive). MTX-loaded nanogels generally exhibit controlled and prolonged drug release compared to free drug, ensuring improved therapeutic efficiency.[37]

Cytotoxicity assays (MTT assay): The cytotoxic potential of nanogel formulations is commonly assessed using the MTT assay on relevant cell lines, such as cancer cells or inflammatory cells. This assay measures cell viability based on mitochondrial activity. MTX-loaded nanogels often demonstrate enhanced cytotoxicity against target cells due to improved cellular uptake and sustained drug release, while showing reduced toxicity toward normal cells.[38]

Cellular uptake studies: Cellular uptake is evaluated using techniques such as fluorescence microscopy or flow cytometry. These studies confirm the internalization of nanogels into cells and help assess the efficiency of targeted delivery. Surface-modified nanogels generally show higher uptake due to receptor-mediated endocytosis, indicating improved targeting capability.[39]

7.2 In Vivo Studies

In vivo studies provide critical insights into the biological performance, safety, and therapeutic effectiveness of MTX nanogel systems in animal models.

Pharmacokinetics: Pharmacokinetic studies evaluate parameters such as absorption, distribution, metabolism, and elimination of the drug. Nanogel formulations typically show prolonged circulation time, reduced clearance, and improved plasma half-life compared to conventional MTX, leading to enhanced drug availability.[40]

Biodistribution studies: These studies assess the distribution of MTX within different organs and tissues. Nanogels demonstrate preferential accumulation at target sites, such as tumors or inflamed tissues, due to the enhanced permeability and retention (EPR) effect and active targeting mechanisms. Reduced accumulation in vital organs like the liver and kidneys indicates lower systemic toxicity.[41]

Therapeutic efficacy: The overall therapeutic performance is evaluated by measuring parameters such as tumor regression, reduction in inflammation, or improvement in disease markers. MTX-loaded nanogels have shown superior efficacy in various experimental models, attributed to targeted delivery, controlled drug release, and improved bioavailability.[42]

Table 3: Summary of Nanogel-Based MTX Studies.[43]

Study Model	Nanogel Type	Polymer Used	Evaluation Method	Key Findings
In vitro (MCF-7 cells)	pH-sensitive nanogel	Chitosan	Drug release, MTT assay	Enhanced cytotoxicity an d controlled release
In vitro (HeLa cells)	Thermoresponsive nanogel	PNIPAM	Cytotoxicity assay	Temperature- triggered drug release
In vitro (fibroblast cells)	Polymer nanogel	PEG	Biocompatibility study	Low toxicity to normal cells
In vitro (cancer cells)	Hybrid nanogel	PEG + PLGA	Cellular uptake study	Improved internalization
In vitro (tumor cells)	Redox-sensitive nanogel	PEG-based	Drug release assay	Triggered release in tumor conditions
In vivo (rat model)	Chitosan nanogel	Chitosan	Pharmacokinetics	Increased half-life and circulation time
In vivo (mouse tumor model)	Targeted nanogel	PEG + ligand	Biodistribution	Higher tumor accumulation
In vivo (arthritic rats)	Thermoresponsive nanogel	PNIPAM	Anti-inflammatory study	Reduced joint inflammation
In vivo (tumor-bearing mice)	Magnetic nanogel	Iron oxide + polymer	Targeting study	Improved site- specific delivery
In vitro/in vivo	Injectable nanogel	PEG-based	Drug release & efficacy	Sustained drug release profile
In vivo (rat model)	Biodegradable nanogel	PLGA	Toxicity study	Reduced systemic toxicity
In vitro (cell lines)	Surface-modified nanogel	Ligand-functionalized	Uptake study	Enhanced receptor-mediated uptake
In vivo (cancer model)	Smart nanogel	Multi-polymer	Therapeutic evaluation	Improved anticancer activity
In vitro (drug release model)	Hydrogel nanoparticle	PVA	Release kinetics	Prolonged drug release
In vivo (mouse model)	Enzyme-responsive nanogel	Gelatin	Efficacy study	Site-specific drug Release and improved outcomes

8. MECHANISM OF NANOGEL-MEDIATED DRUG DELIVERY

Nanogel-mediated drug delivery involves a series of coordinated processes that enhance the therapeutic performance of methotrexate (MTX) by improving its stability, targeting efficiency, and controlled release.

Drug encapsulation and protection: Methotrexate is encapsulated within the three-dimensional polymeric network of nanogels through physical entrapment or chemical conjugation. This encapsulation protects the drug from premature degradation, enzymatic inactivation, and rapid systemic clearance. The hydrated structure of nanogels also enhances drug stability and solubility, ensuring efficient delivery to the target site.[44]

Targeted accumulation at disease site: Nanogels accumulate preferentially at diseased tissues through passive and active targeting mechanisms. Passive targeting occurs via the enhanced permeability and retention (EPR) effect, where nanogels penetrate and retain within tumor or inflamed tissues due to leaky vasculature. Active targeting is achieved by surface modification of nanogels with ligands, antibodies, or peptides that specifically bind to receptors overexpressed on target cells, thereby increasing localization and therapeutic precision.[45]

Controlled release mechanism: Once accumulated at the target site, nanogels release methotrexate in a controlled manner. This release can occur through diffusion, degradation of the polymer network, or in response to specific stimuli such as pH, temperature, enzymes, or redox conditions. Stimuli-responsive nanogels ensure that drug release occurs specifically at the disease site, minimizing systemic exposure and enhancing therapeutic efficacy.[46]

Cellular internalization pathways: Nanogels enter target cells primarily through endocytosis mechanisms, including clathrin-mediated, caveolae-mediated, or receptor-mediated endocytosis. Following internalization, the nanogels release MTX intracellularly, allowing it to interact with its molecular target (DHFR) and exert its pharmacological effect. This efficient cellular uptake significantly enhances drug bioavailability at the cellular level.[47]

Overall, nanogel-mediated delivery provides a multi-step, highly controlled mechanism that improves drug targeting, minimizes toxicity, and enhances the therapeutic outcomes of methotrexate.

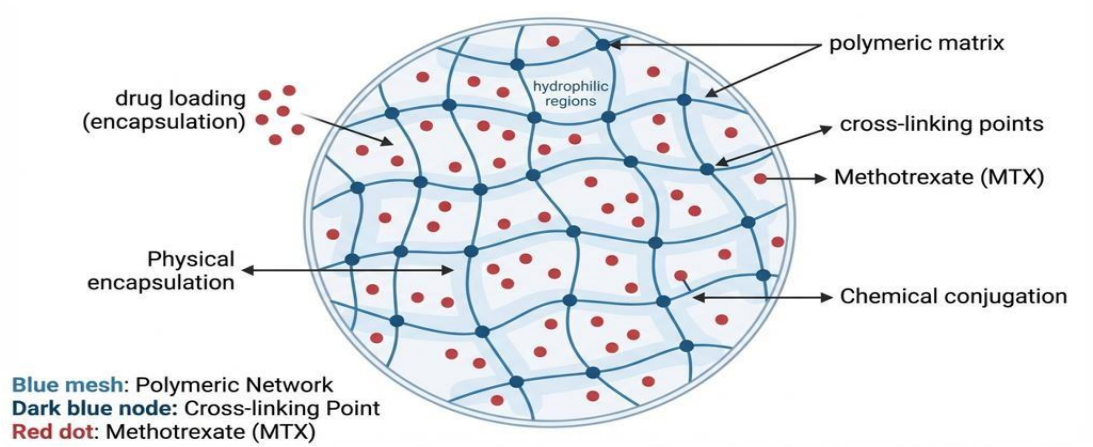

Figure 1: Structure and Drug Loading Mechanism of Nanogels[48]

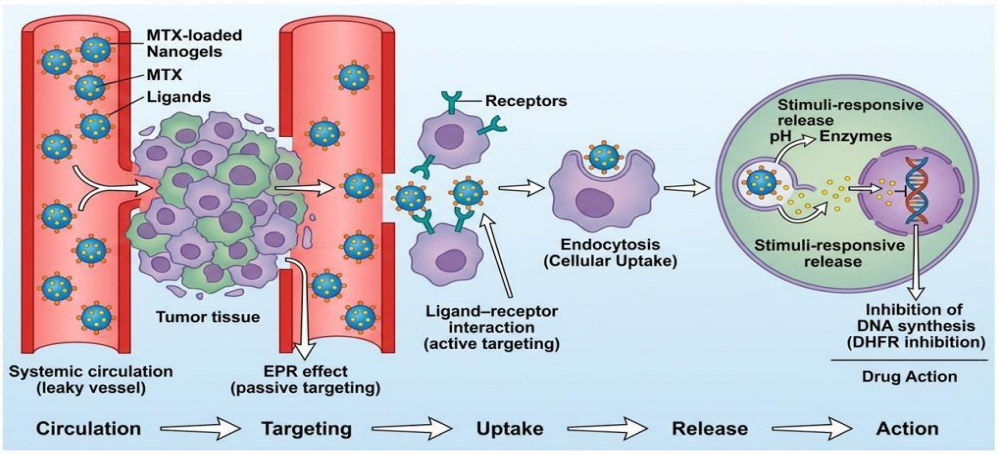

Figure 2: Mechanism of Targeted Methotrexate Delivery via Nanogels[49]

9. FORMULATION CHALLENGES AND SAFETY CONSIDERATIONS

Despite the promising potential of nanogel-based systems for methotrexate (MTX) delivery, several formulation and safety-related challenges must be addressed to ensure successful clinical translation.

Stability issues: Nanogels may face physical and chemical instability during storage and in biological environments. Factors such as aggregation, premature drug leakage, and degradation of the polymer network can affect their performance. Maintaining structural integrity, drug retention, and reproducibility over time remains a critical challenge, requiring optimization of formulation parameters and storage conditions.[50]

Scale-up challenges: While nanogels demonstrate excellent performance at the laboratory scale, translating these systems to large-scale manufacturing is complex. Issues such as batch-to-batch variability, reproducibility, cost-effectiveness, and process standardization hinder industrial production. Developing scalable, robust, and economically feasible fabrication methods is essential for commercialization.[51]

Polymer toxicity concerns: Although many polymers used in nanogels are considered biocompatible, their long-term safety profile must be thoroughly evaluated. Degradation products, residual cross-linking agents, and synthetic polymer components may induce toxicity, immunogenicity, or inflammatory responses. Careful selection of biodegradable and non-toxic polymers, along with comprehensive toxicological studies, is necessary to ensure patient safety.[52]

Regulatory barriers: Nanogel-based drug delivery systems face stringent regulatory requirements due to their complex structure and multifunctional nature. Lack of standardized guidelines for nanomedicines, variability in characterization methods, and limited long-term clinical data pose significant hurdles in regulatory approval. Addressing these challenges requires well-defined quality control measures, extensive preclinical and clinical validation, and adherence to regulatory frameworks.[53]

Overall, overcoming these challenges is crucial for the successful development, approval, and clinical application of nanogel-based methotrexate delivery systems.

10. FUTURE PERSPECTIVES

The field of nanogel-based drug delivery for methotrexate (MTX) is rapidly evolving, with several emerging strategies expected to enhance its clinical applicability and therapeutic performance.

Development of smart nanogels: Future research is increasingly focused on designing smart or stimuli-responsive nanogels capable of precise, on-demand drug release. These systems can respond to multiple physiological triggers such as pH, temperature, enzymes, or redox conditions, enabling highly controlled and site-specific delivery. Advanced multifunctional nanogels integrating targeting ligands and imaging agents are also being explored for theranostic applications.

Personalized medicine approaches: Nanogel platforms offer significant potential in personalized medicine by enabling patient-specific drug delivery strategies. Tailoring nanogel formulations based on disease type, severity, and individual patient characteristics can optimize therapeutic outcomes while minimizing adverse effects. Integration with biomarker-based targeting and precision diagnostics is expected to further enhance treatment efficacy.

Clinical translation challenges: Although preclinical studies have demonstrated promising results, the transition of nanogel systems from laboratory to clinical practice remains a major challenge. Issues such as large-scale production, reproducibility, long-term safety, and regulatory approval need to be systematically addressed. Establishing standardized protocols and conducting well-designed clinical trials are essential steps toward successful translation.

Combination therapies: Nanogels provide an excellent platform for co-delivery of multiple therapeutic agents, such as combining methotrexate with anti-inflammatory drugs, chemotherapeutics, or biological agents. Such combination therapies can produce synergistic effects, improve treatment efficacy, and reduce drug resistance. This approach holds great promise, particularly in complex diseases like cancer and autoimmune disorders.

Overall, continued advancements in nanotechnology, material science, and biomedical research are expected to drive the development of innovative nanogel systems, paving the way for more effective and safer methotrexate therapies in the future.

11. CONCLUSION

Nanogel-based drug delivery systems have emerged as a highly promising and innovative platform for improving the therapeutic performance of methotrexate (MTX). By overcoming key limitations associated with conventional MTX therapy—such as poor bioavailability, non- specific distribution, and systemic toxicity—nanogels offer a more efficient and targeted approach to drug delivery. Their unique properties, including high biocompatibility, tunable structure, and stimuli-responsive behavior, enable controlled and sustained drug release, leading to enhanced therapeutic outcomes.

The application of nanogels in MTX delivery has demonstrated significant improvements in drug stability, bioavailability, and site-specific targeting, while simultaneously reducing adverse effects. These advantages contribute to better treatment efficacy and improved patient safety, particularly in chronic conditions and cancer therapy.

However, despite encouraging preclinical findings, the clinical translation of nanogel-based systems remains limited. There is a critical need for extensive clinical validation, standardized formulation protocols, and comprehensive safety assessments to ensure their successful integration into clinical practice.

In conclusion, nanogels hold substantial potential as advanced drug delivery carriers for methotrexate, and continued research efforts are essential to fully realize their role in modern therapeutics and precision medicine.

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