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Review

Design of Nanogel Formulation of Naproxen for Enhanced Anti-Inflammatory Effect: A Comprehensive Review

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Abstract

As a commonly prescribed nanogel, naproxen is an NSAID used in the treatment of many acute and chronic inflammatory conditions. But because of poor aqueous solubility, side effects related to the gastrointestinal tract after oral use, and poor skin permeation with regular topical treatments, its clinical use is limited. Recent literature in PubMed reports nanogel-based drug delivery systems as a promising means to overcome these obstacles by improving drug solubility and skin penetration as well as providing controlled and sustained drug release at the target site for inflammation. This review examines the design principles, selections of polymers, formulation methodologies, characterization methodologies, and naproxen-loaded nanogel systems anti-inflammatory activities for nanogels. Advanced safety features and clinical application of naproxen nanogel formulations, as well as naproxen's release from the nanogel, will also be discussed.

Keywords: Naproxen; Nanogels; Topical drug delivery; Anti-inflammatory therapy; NSAIDs; Skin permeation

1. Introduction

Inflammation is an over-simplification of tissue damage, and affects body tissues, infections, and the immune system. Some disorders related to inflammation are arthritis, rheumatoid arthritis, osteoporosis, and many more

disorders related to pain of the structure of the body. Considering the disruption of the pain and inflammation, non-steroidal anti-inflammatory drugs, simple inflammatory pain and cyclooxygenase are the coping mechanisms, and pain and inflammation management; so, non-steroidal anti-inflammatory drugs seem to be the most common. [1]

Naproxen exhibits a anti-inflammatory, analgesic. febrile reaction and enabling propionic acid [2]. Side effects of prolonged naproxen are cardiac, systemic adverse effects and integumentary are some of the things seen. There is a positive impact of topical naproxen; concentrating to the inflamed area averts systemic naproxen, still, topical delivery naproxen has some challenges.

There is a pain that is considered to be psychosomatic that provides the opportunity to target the pain directly. Ant dangerously collaborates deceptive pain. Pain of the application and Psychosomatic pain are barriers that are, diffusing the pain, and the opportunity to target and surpass the pain. Assuming that the provided psychosomatic pain is enhanced. Some are some psychological barriers with pain that is deceiving the application, and that pain. There has to be more advanced systems with free, prolonged local pain, counteract pain, and prolonged psychosomatic pain are some of the barriers seen with pain [3]. Those psychosomatic barriers that are seen are advanced systems.

2. Nanogels as Advanced Drug Delivery Systems

Nanogels are nanosized hydrogel particles made of interconnected polymer networks. They can hold larger amounts of water or biological fluids due to their unique structure. Usually, they are sized at nanoscale: 20-500 nm and can contain both water-soluble and insoluble drugs. Nanogels are nanoscale, three-dimensional crosslinked polymer networks capable of encapsulating both hydrophilic and hydrophobic drugs. Due to their small particle size, high water content, and tunable physicochemical properties, nanogels have emerged as advanced drug delivery systems with significant potential in pharmaceutical and biomedical applications.

One of the key advantages of nanogels is their high drug-loading capacity and ability to protect encapsulated drugs from degradation. Their soft and flexible structure allows close interaction with biological membranes, facilitating enhanced penetration through physiological barriers such as the skin. Additionally, nanogels can provide controlled and sustained drug release, reducing dosing frequency and improving patient compliance.

Nanogels can be engineered using natural or synthetic polymers, including chitosan, alginate, poly(N-isopropylacrylamide), and Carbopol derivatives. Their responsiveness to external stimuli such as pH, temperature, or ionic strength enables site-specific and triggered drug release. This property is particularly advantageous for topical, transdermal, and targeted drug delivery applications.

Overall, nanogels represent a promising platform for advanced drug delivery due to their biocompatibility, versatility, and ability to enhance drug stability and therapeutic efficacy. Ongoing research continues to explore their potential in improving the delivery of poorly soluble drugs and achieving controlled release profiles.

2.1. Benefits of Nanogels

Nanogels of all types bring positive advancements toward actionable steps in topical drug delivery:

- Provides improved solubility for drugs previously thought to be poorly soluble in water
- Higher rates of skin penetration due to smaller particle sizes
- Provides for more prolonged drug delivery in a controlled manner
- Greater levels of biocompatibility and biodegradability
- Potential for responsive drug release based on stimuli

These innovations make nanogels especially useful for the therapy of localized inflammation. [6]

2.2. Types of Nanogels

Nanogels can be categorized based on the structures of the polymers used in the materials and the response to stimuli.

- Polymeric nanogels, be these synthetic or biopolymeric materials
- Stimuli responsive (pH, temperature, or enzymatic) nanogels
- Hybrids of nanogels (combinations of, polymer-lipid or polymer with inorganic systems)

Stimuli responsive nanogels hold great promise for the controlled release of drugs in inflamed microenvironments. [7]

3. Rationale for the Nanogel Delivery of Naproxen

1. **Enhanced Solubility and Bioavailability**
   Naproxen, a nonsteroidal anti-inflammatory drug (NSAID), has limited water solubility, which can restrict its absorption in the gastrointestinal tract. Incorporating Naproxen into a nanogel can improve its solubility, leading to better absorption and enhanced bioavailability. Nanogels can encapsulate hydrophobic drugs and maintain them in a stable, dispersed form.
2. **Controlled and Sustained Drug Release**
   Nanogels can be engineered to release Naproxen gradually over time, reducing the frequency of dosing and maintaining therapeutic drug levels in the body. This sustained release can also minimize the peak-trough fluctuations associated with conventional oral Naproxen, which can help in reducing side effects.
3. **Targeted Delivery and Reduced Side Effects**
   Nanogels have the potential to deliver drugs selectively to specific tissues or sites of inflammation. This targeted approach can decrease systemic exposure, thereby reducing common NSAID-related side effects such as gastric irritation, ulceration, and renal toxicity.
4. **Improved Patient Compliance**
   By offering controlled release and potentially reducing side effects, nanogel formulations can improve patient adherence to therapy. A once-daily or less frequent dosing regimen is more convenient compared to standard formulations.
5. **Versatility and Stability**
   Nanogels are highly versatile and can be tailored in terms of size, surface charge, and responsiveness to environmental stimuli (like pH or temperature). This makes them suitable for delivering Naproxen in various forms, including oral, topical, or injectable routes, while maintaining drug stability.
6. **Protection of Drug from Degradation**
   Naproxen may degrade under certain physiological conditions. Encapsulation within a nanogel can protect it from chemical or enzymatic degradation, ensuring that the drug reaches its target site in an active form. [7]

In short**,** nanogel delivery systems for Naproxen aim to improve solubility, enhance bioavailability, provide controlled release, reduce side effects, and increase therapeutic efficiency**,** making the treatment safer and more effective.

The low bioavailability of topical naproxen and its efficacy is mainly from the drug's characteristics, namely a low solubility in water and its propensity for high plasma protein binding. Naproxen's solubility can increase with the help of nanogels that incorporate the polymeric networks and promote skin barrier penetration. [8]

Additionally, compared to older topical formulations, nanogels produce sustained release of drug in the formed polymeric network. This results in prolonged drug residence time in the target tissue, a greater tissue damping of the inflammatory mediators, and overall enhanced therapeutic efficacy. [9]

4. Design Considerations for Naproxen Nanogels

4.1. Polymer Selection

Polymer selection plays a critical role in the design and performance of nanogel-based drug delivery systems. The choice of polymer influences key formulation characteristics, including particle size, drug-loading capacity, release behavior, stability, and biocompatibility. Both natural and synthetic polymers are commonly used in nanogel formulation due to their versatility and favorable physicochemical properties.

Natural polymers such as chitosan, alginate, gelatin, and hyaluronic acid are widely preferred for their biocompatibility, biodegradability, and low toxicity. These polymers can enhance skin adhesion and improve drug permeation in topical and transdermal applications. Synthetic polymers, including poly(N-isopropylacrylamide), poly(lactic-co-glycolic acid), and Carbopol derivatives, offer better control over molecular weight, crosslinking density, and stimuli responsiveness.

The polymer must be compatible with the drug and other formulation components while maintaining stability under physiological conditions. Additionally, the polymer should allow efficient gel formation, appropriate viscosity, and controlled drug release. Therefore, careful polymer selection is essential to ensure the safety, efficacy, and overall performance of nanogel drug delivery systems.

Polymer selection is a critical factor in nanogel formulation. Commonly used polymers for naproxen nanogels include:

- Poly(acrylic acid) derivatives (e.g., Carbopol)
- Chitosan
- Sodium alginate
- Poly(N-isopropylacrylamide) (PNIPAM)

These polymers offer desirable properties such as biocompatibility, swelling ability, and controlled drug release behaviour. [10]

4.2. Cross-Linking Density

Cross-linking density is a crucial parameter influencing the structural integrity and functional performance of nanogel-based drug delivery systems. It determines the mesh size of the polymer network, which directly affects drug encapsulation efficiency, swelling behavior, mechanical strength, and release kinetics.

An increase in cross-linking density generally results in a tighter polymer network with reduced pore size, leading to enhanced structural stability and slower drug diffusion. Conversely, lower cross-linking density produces a more flexible and highly swollen network, allowing higher drug loading and faster drug release. Therefore, optimizing cross-linking density is essential to achieve a balance between formulation stability and desired release profiles.

The selection of cross-linking agents and their concentration must be carefully controlled to ensure biocompatibility and minimize potential toxicity. Appropriate cross-linking density also influences the responsiveness of nanogels to external stimuli such as pH, temperature, or ionic strength, enabling controlled and targeted drug delivery. Thus, precise regulation of cross-linking density is critical for the effective design of nanogel drug delivery systems.

The degree of cross-linking is influenced by nanogel particle size, drug entrapment efficiency, and release kinetics. The optimized cross-linking ensures structural stability while allowing sufficient swelling for drug diffusion. [11]

4.3. Particle Size and Surface Charge

Particle size below 300 nm is considered as optimal for topical delivery. Surface charge affects nanogel stability and interaction with skin lipids. Mildly charged nanogels demonstrate enhanced adhesion to the skin surface and improved permeation. Particle size distribution and morphological characteristics of the formulation are evaluated using dynamic light scattering (DLS) and transmission electron microscopy (TEM). DLS is employed to determine the average particle size, polydispersity index (PDI), and size distribution, providing insight into the uniformity and stability of the nanoparticulate system.Transmission electron microscopy (TEM) is used to visualize particle shape and surface characteristics at the nanoscale, allowing direct observation of particle morphology and confirmation of size obtained from DLS analysis. Together, these techniques provide comprehensive characterization of the nanodispersion, ensuring consistency and suitability for topical or transdermal drug delivery applications.[12]

5. Formulation Strategies for Naproxen Nanogels

5.1. Preparation Techniques

Nanogels can be prepared using various techniques depending on the type of polymer, drug properties, and desired particle characteristics. Common preparation methods include emulsion polymerization, inverse miniemulsion, nanoprecipitation, and ionic gelation. Each technique offers distinct advantages in controlling particle size, cross-linking density, and drug-loading efficiency.

Emulsion polymerization involves the formation of nanogels through polymerization of monomers within emulsion droplets, enabling precise control over particle size and uniformity. Inverse miniemulsion techniques are particularly useful for encapsulating hydrophilic drugs, as the polymerization occurs within nanosized aqueous droplets dispersed in an organic phase. Nanoprecipitation is a simple and solvent-based method that produces nanogels through rapid mixing of polymer and non-solvent, resulting in spontaneous particle formation.

Ionic gelation is widely employed for natural polymers such as chitosan and alginate, where cross-linking occurs through electrostatic interactions with multivalent ions. This method is mild, avoids harsh solvents, and is suitable for heat- or pH-sensitive drugs. Selection of an appropriate preparation technique is essential to achieve optimal nanogel properties, stability, and therapeutic performance.

There are Several techniques have been reported for nanogel preparation, including:

- Emulsification–diffusion
- Nanoprecipitation
- Ultrasonication
- In situ polymerization. [13]

5.2. Conversion into Gel Systems

Nanodispersions are often incorporated into gel bases such as Carbopol 934 or 940 to improve viscosity, spreadability, and patient acceptability. pH adjustment ensures compatibility with skin physiology. Nanodispersions are frequently incorporated into suitable gel bases to enhance their rheological properties and patient acceptability. Polymers such as Carbopol 934 or Carbopol 940 are commonly used due to their excellent gelling ability, transparency, and compatibility with topical formulations. Incorporation of nanodispersions into these gel matrices improves viscosity and spreadability, facilitating uniform application and prolonged residence time at the site of application.Additionally, gel systems enhance the stability of the formulation and provide better control over drug release. pH adjustment of the gel, typically using neutralizing agents such as triethanolamine or sodium hydroxide, is essential to ensure compatibility with skin physiology and to minimize the risk of irritation. Maintaining the formulation pH within the physiological range promotes patient comfort

and improves therapeutic efficacy, making nanodispersion-based gels a promising approach for topical drug delivery. [14]

5.3. Penetration Enhancement Strategies

- ✓ The Chemical penetration enhancers such as oleic acid, ethanol, and propylene glycol are frequently incorporated to disrupt the stratum corneum lipid structure and enhance naproxen permeation. **"Penetration Enhancement Strategies** Chemical penetration enhancers such as oleic acid, ethanol, and propylene glycol are commonly incorporated to disrupt the lipid structure of the stratum corneum, thereby enhancing the permeation of naproxen."
- ✓ If you want it **simpler**, **more detailed**, or **more technical**, tell me the style you need (e.g., thesis, journal article, presentation).
- ✓ Penetration Enhancement Strategies The Chemical penetration enhancers such as oleic acid, ethanol, and propylene glycol are frequently incorporated to disrupt the stratum corneum lipid structure and enhance naproxen permeation articcccle cconteent

  Here is **expanded article-style content** suitable for a **pharmaceutics / drug delivery research article**:

- ✓ The stratum corneum acts as the primary barrier to transdermal drug delivery due to its highly organized lipid matrix. To overcome this barrier and improve drug permeation, chemical penetration enhancers are widely employed in topical and transdermal formulations. Commonly used enhancers include oleic acid, ethanol, and propylene glycol, each of which enhances permeation through distinct mechanisms.
- ✓ Oleic acid functions by disrupting the ordered lipid domains of the stratum corneum, increasing lipid fluidity and creating microchannels that facilitate drug diffusion. Ethanol acts as a solvent and permeation enhancer by extracting lipids from the stratum corneum and improving drug solubility within the skin layers. Propylene glycol enhances penetration by increasing skin hydration and acting as a co-solvent, thereby improving drug partitioning into the skin.
- ✓ The incorporation of these chemical penetration enhancers has been shown to significantly improve the transdermal permeation of naproxen, a nonsteroidal anti-inflammatory drug (NSAID) with limited skin permeability. By modifying the barrier properties of the stratum corneum, these enhancers increase drug flux and promote effective drug delivery across the skin, making them valuable components in topical naproxen formulations. [15]

6. Characterization of Naproxen Nanogels

6.1. Particle

Nanodispersions are frequently incorporated into suitable gel bases to enhance their rheological properties and patient acceptability. Polymers such as Carbopol 934 or Carbopol 940 are commonly used due to their excellent gelling ability, transparency, and compatibility with topical formulations. Incorporation of nanodispersions into these gel matrices improves viscosity and spreadability, facilitating uniform application and prolonged residence time at the site of application. Additionally, gel systems enhance the stability of the formulation and provide better control over drug release. pH adjustment of the gel, typically using neutralizing agents such as triethanolamine or sodium hydroxide, is essential to ensure compatibility with skin physiology and to minimize the risk of irritation. Maintaining the formulation pH within the physiological range promotes patient comfort and improves therapeutic efficacy, making nanodispersion-based gels a promising approach for topical drug delivery. Particle size and morphology are critical parameters that influence the stability, drug release, and skin penetration of naproxen-loaded nanogels. Dynamic Light Scattering (DLS) is commonly used to measure the average particle size, polydispersity index (PDI), and size distribution of nanogels, providing insight into formulation uniformity and stability. A low PDI indicates a homogeneous system, which is essential for reproducible drug delivery.

Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) are used to visualize the shape, surface characteristics, and morphology of the nanoparticles. TEM provides high-resolution images that

confirm particle size and spherical or irregular morphology, while SEM gives information on surface texture and aggregation behavior. Together, these techniques ensure that the nanogels meet the desired specifications for effective topical or transdermal delivery of naproxen. [16]

6.2. Drug Loading and Entrapment Efficiency

High drug entrapment efficiency indicates effective encapsulation of naproxen within the nanogel matrix, contributing to sustained release.

Drug loading and entrapment efficiency are key parameters for evaluating the effectiveness of naproxen nanogels. **Drug loading** refers to the amount of drug incorporated per unit weight of nanogel, while **entrapment efficiency** represents the percentage of the initial drug successfully encapsulated within the nanogel matrix.

High entrapment efficiency indicates that naproxen is effectively incorporated into the polymer network, which helps protect the drug from degradation and minimizes premature release. Optimized drug loading ensures that therapeutic concentrations can be delivered over a sustained period, enhancing efficacy while reducing dosing frequency. Factors such as polymer type, cross-linking density, and preparation technique play a crucial role in determining the encapsulation efficiency.

Overall, high drug loading and entrapment efficiency are essential for the development of stable, effective nanogel formulations suitable for topical or transdermal administration. [17]

6.3. Rheological Properties

Rheological evaluation is essential for assessing the flow behavior, spreadability, and overall applicability of naproxen nanogels. The viscosity and viscoelastic properties of the gel influence its ease of application, skin adhesion, and drug release profile.

Viscosity measurements are typically performed using a rotational viscometer, which provides information on the gel's resistance to flow under different shear rates. Most nanogels exhibit **pseudoplastic (shear-thinning) behavior**, meaning viscosity decreases under shear stress, facilitating easy spreading on the skin while maintaining stability at rest.

Viscoelastic properties, determined through oscillatory rheology, give insight into the gel's structural integrity and recovery after deformation. An optimized balance between elastic and viscous behavior ensures that the nanogel maintains contact with the skin long enough to allow sustained drug release while remaining user-friendly.

Additionally, rheological properties can be modulated by adjusting polymer concentration, cross-linking density, or incorporation of co-solvents, making them a critical parameter in the design of effective naproxen nanogels.

Rheological evaluation ensures appropriate viscosity, spread ability, and mechanical stability of nanogels for topical application. [18]

6.4. In Vitro Drug Release

Naproxen nanogels typically exhibit sustained drug release over 12–24 h, following diffusion-controlled or swelling-controlled kinetics. [19]

6.5. Ex Vivo Skin Permeation Studies

Franz diffusion cell studies using animal or human skin models demonstrate significantly enhanced drug permeation from nanogels compared to conventional gels. [20]

7. Anti-Inflammatory Activity

In vivo studies using carrageenan-induced paw edema models have confirmed superior anti-inflammatory activity of naproxen nanogels. Enhanced efficacy is attributed to improved skin penetration and prolonged drug retention at the inflamed site. [21]

8. Safety and Toxicological Evaluation

Naproxen nanogels formulated using biocompatible polymers show minimal skin irritation and reduced systemic absorption. These characteristics support their suitability for long-term topical therapy. [22]

9. Future Perspectives

Future research should focus on:

- Clinical evaluation of naproxen nanogels
- Scale-up and manufacturing feasibility
- Development of smart stimuli-responsive nanogels
- Regulatory considerations for nanomedicine products

Advances in polymer science and nanotechnology are expected to further enhance the clinical potential of nanogel-based NSAID delivery systems. [23]

Property	Purpose	Method
Particle size	Drug release, uptake	DLS, TEM, SEM
Zeta potential	Stability	Zetasizer
Drug loading & EE	Formulation efficiency	UV-Vis, HPLC
Morphology	Shape, surface	SEM, TEM, AFM
Swelling	Release mechanism	Buffer incubation, gravimetry
Drug release	Therapeutic profile	Dialysis, dissolution test
FTIR	Drug-polymer interactions	FTIR spectroscopy
DSC	Thermal behavior	Differential scanning calorimetry
XRD	Crystallinity	X-ray diffraction
Stability	Shelf-life	Temperature storage study

10. Conclusions

Nanogel-based formulations are a promising way to improve the topical delivery and anti-inflammatory effects of naproxen. Nanogels get around the problems with traditional dosage forms by making drugs more soluble, easier to get through the skin, and longerlasting. Ongoing research and clinical validation may confirm naproxen nanogels as viable alternatives for localized anti-inflammatory treatment.

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