FORMULATION AND EVALUATION OF MESOPOROUS SILICA NANOPARTICLES LOADED ANTIARTHRITIC GEL AS A TARGETED DRUG DELIVERY SYSTEM

फार्मूलेशन एंड इवैल्यूएशन ऑफ़ मेसोपोरोस सिलिका नैनोपार्टिकल्स लोडेड एंटीअर्थरिटिक जेल एज अ टार्गेटेड ड्रग डिलीवरी सिस्टम

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Abstract

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ABSTRACT

The thesis entitled **"Formulation and Evaluation of mesoporous silica nanoparticles loaded antiarthritic gel as a targeted drug delivery system"** contains the research work carried out for Ph.D. Degree, at Pacific University of Higher Education and Research, Rajasthan, India under the supervision of **Dr. Rakte Amol Sharanappa** and under Co-Supervision of **Dr. Vishal Vijay Pande**.

This system aims to improve the solubility, permeability, and bioavailability of poorly soluble drugs and enhance the targeted delivery to arthritic sites, thereby maximizing therapeutic efficacy while minimizing systemic side effects.

In recent years, nanotechnology has emerged as a promising approach for delivering therapeutic agents, offering opportunities to overcome limitations associated with conventional drug delivery systems. Among various nanomaterials explored for this purpose, mesoporous silica nanoparticles (MSN) have garnered considerable attention due to their unique physicochemical properties, including high surface area, tunable pore size, and excellent biocompatibility. These characteristics make MSN ideal candidates for encapsulating and delivering a wide range of therapeutic compounds, including poorly soluble drugs. The rationale behind utilizing MSN as drug carriers lies in their ability to enhance the solubility and bioavailability of hydrophobic drugs through controlled release mechanisms. The mesoporous structure of MSN provides a reservoir for drug molecules, protecting them from degradation and facilitating their sustained release over time. Furthermore, the surface of MSN can be functionalized to tailor drug loading and release properties, allowing precise control over drug delivery kinetics.

In this study, we focus on two therapeutic agents, methotrexate and tofacitinib citrate. Methotrexate is commonly used in the treatment of various cancers and autoimmune diseases also it is considered as first choice for treatment of rheumatoid arthritis, while tofacitinib citrate is indicated for the management of rheumatoid arthritis and ulcerative colitis. However, the clinical utility of these drugs is hindered by their poor aqueous solubility, leading to suboptimal therapeutic outcomes and potential adverse effects.

Methotrexate and Tofacitinib Citrate, when incorporated into the MSN-based gel, can potentially offer significant improvements in drug delivery. The high surface area and controlled release properties of MSNs allow for targeted delivery of these drugs to the affected joints, enhancing their therapeutic efficacy while reducing systemic side effects. This approach not only addresses the limitations associated with oral drug administration but also provides a more convenient and effective treatment option for patients suffering from arthritis

The whole thesis was divided into seven chapters as follows:

Chapter 1: Introduction

In this chapter gives information about Arthritis and its different aspects and treatments, Mesoporous silica Nanoparticles (MSNs) as a effective drug carrier, Use of Nanogel for Targeted drug delivery system.

Arthritis, a group of inflammatory joint disorders, affects millions worldwide. Effective pain management of arthritis often requires prolonged treatment with antiarthritic medications. Two commonly used drugs in the treatment of arthritis are Methotrexate and Tofacitinib Citrate. Methotrexate is a disease-modifying anti-rheumatic drug (DMARD) that inhibits cellular metabolism and reduces inflammation, making it a cornerstone in the treatment of rheumatoid arthritis. Tofacitinib Citrate, is a Janus kinase (JAK) inhibitor that interferes with specific intracellular signaling pathways to diminish the inflammatory response.

Mesoporous silica nanoparticles (MSNs) have emerged as highly effective drug carriers due to their unique properties. MSNs are characterized by their high surface area, tunable pore size, and ability to provide controlled release of encapsulated drugs. These attributes make MSNs ideal candidates for drug delivery systems that require targeted and sustained release.

Topical gels are a promising method for localized drug delivery in arthritis treatments. Arthritis is often characterized by inflammation and pain in the joints, making it important to deliver medications directly to the affected area. Gels provide an ideal medium for this because of their semi-solid nature and ease of application. They spread easily over the skin, forming a thin film, which ensures better contact between the drug and the skin surface.

Chapter 2: Review of literature

In this chapter important literatures were done to understood the effectiveness of MSNs as drug carrier and systemic limitations of conventional drug delivery of Methotrexate and Tofacitinib citrate in the treatment of arthritis. To design the research work in detail.

Methotrexate and Tofacitinib Citrate, when incorporated into the MSN-based gel, can potentially offer significant improvements in drug delivery. The high surface area and controlled release properties of MSNs allow for targeted delivery of these drugs to the affected joints, enhancing their therapeutic efficacy while reducing systemic side effects. This approach not only addresses the limitations associated with oral drug administration but also provides a more convenient and effective treatment option for patients suffering from arthritis.

Chapter 3: Aim and Objectives

The aim of this research is to formulate and evaluate a mesoporous silica nanoparticle (MSN)-based antiarthritic gel as a targeted drug delivery system- to improve the solubility, permeability, and bioavailability of poorly soluble drugs and enhance the targeted delivery to arthritic sites, thereby maximizing therapeutic efficacy while minimizing systemic side effects.

Objectives:

1. **Synthesis, Surface modification and Characterization of Mesoporous Silica Nanoparticles (MSNs):** MSNs will act as the drug carriers due to their high surface area, tunable pore sizes, and excellent biocompatibility.

   Characterization of MSNs: using techniques such as

   - **Fourier-Transform Infrared Spectroscopy (FTIR): (**presence of characteristic peaks for organic functional groups indicates successful surface modification.)
   - **Differential Scanning Calorimetry (DSC)** (for thermal properties),
   - **Scanning Electron Microscopy (SEM)** and **Transmission Electron Microscopy (TEM)** (to study nanoparticle morphology),

- **Brunauer-Emmett-Teller (BET) analysis** (to measure the surface area of MSNs).
- **pXRD** (to understand structural integrity and crystallinity)

2. **Loading of Antiarthritic Drugs into surface modified MSNs:** This step will focus on improving the drug's solubility and dissolution rate of poorly soluble drugs to ensure efficient drug delivery.
3. **Formulation of MSN-Loaded Nanogel:** This objective focuses on the formulation of a topical gel incorporating MSN-loaded antiarthritic drugs to create a targeted drug delivery system to ensure the drug is released at the desired site of action (arthritic joints), enhancing local bioavailability while minimizing systemic exposure.
4. **Characterization of the MSN-Loaded Nanogel:** using advanced techniques such as:
   - Viscosity
   - Spreadability
   - Texture analysis
   - Particle size and Particle size distribution
   - Zeta potential
   - Drug release profile
5. **Stability of the antiarthritic Nanogel**

   To establish the good shelf life and to provide flexibility in storage options.

6 **Dermatokinetics Study:** The final objective is to perform dermatokinetic of the formulated MSN-loaded nanogel. This will provide insight into how well the formulation delivers the drug to the targeted site and its overall therapeutic efficacy.

Chapter 4: Plan of work

This chapter details the plan of work-

1 Selection of drug and excipient (Tofacitinib Citrate and Methotrexate)

2 Synthesis of mesoporous silica i.e. SBA-15

3 Characterization of synthesized SBA-15

4 Amine functionalization of SBA-15

5 Characterization of surface modified Mesoporous Silica

6 Loading of antiarthritic drugs in Surface Modified MSNs

7 Characterization of antiarthritic drugs loaded MSNs

8 Incorporation of MSN's in to gel base to prepare Nanogel

9 Characterization of the MSN-Loaded Nanogel

10 Stability study

11 Dermatokinetic evaluation of Antiarthritic gel

Chapter 5: Materials and methods

This chapter provided the detailed information on the materials and instruments used for manufacturing and evaluation of MSNs and Formulation Nanogel.

Detailed information on Synthesis, Surface modification and Characterization of MSNs was given. Formulation development deals with gel base manufacturing and then incorporation of antiarthritic drug loaded MSN in to gel base. Characterization of gel formulation provided the information on suitability of gel formulation for arthritic treatment for the topical purpose.

Chapter 6: Results and discussion

In this chapter results obtained for Synthesis and characterization of MSNs confirms the desired MSN platform was obtained when evaluated using sophisticated instruments like FTIR, DSC, SEM, TEM, BET, pXRD etc. A honeycomb like regular structure uniform pore sizes, typically in the range of 2 to 50 nm, distributed throughout the silica matrix with suitable surface morphology properties.

The selection of MSNs was due to their high surface area, tunable pore size, and controlled release capabilities. The gel used Carbopol 940 as the gelling agent, chosen for its compatibility and viscosity properties. The formulation process involved dispersing Carbopol 940 in distilled water, hydrating, and adjusting the pH before incorporating the drug-loaded MSNs. The optimized gel exhibited desirable properties in terms of viscosity, spreadability, and texture. Particle size analysis showed a narrow distribution, and zeta potential

measurements confirmed the stability of the gel. *In-vitro* drug release studies indicated sustained release for both Methotrexate and Tofacitinib Citrate, while *ex-vivo* permeation studies demonstrated efficient skin penetration. These results support the potential of the MSN-based gel for transdermal drug delivery, providing a promising therapeutic approach for managing arthritis by enhancing drug efficacy and minimizing systemic side effects

Gel formulation remains stable for all formulation parameters at accelerated conditions, room temperatures and at lower temperatures providing flexibility in storage options.

Chapter 7: Summary and Conclusion

This research presents a novel approach for enhancing the therapeutic efficacy of antiarthritic drugs through advanced nanotechnology. The study comprehensively investigates the structural, morphological, and textural properties of MSNs using various analytical techniques including FTIR spectroscopy, particle size analysis, TEM, SEM, DSC, and BET analysis. These characterizations confirm the successful functionalization and high surface area of MSNs, making them an ideal candidate for targeted drug delivery systems.

The antiarthritic drugs Methotrexate and Tofacitinib Citrate were effectively loaded into the surface-modified MSNs, as confirmed by the combination of FTIR and pXRD analyses, which demonstrated the structural integrity of the MSNs post-drug loading.

The loaded MSNs exhibited high drug loading efficiency and a sustained release profile, which are crucial for improving drug solubility, stability, and targeted delivery, ultimately enhancing therapeutic outcomes for arthritis patients. The *in-vitro* and *ex-vivo* evaluations demonstrated that the MSNs-based formulation could achieve controlled and sustained drug release, highlighting its potential as a robust drug delivery platform.

In conclusion, the formulated MSNs-loaded antiarthritic gel offers a promising approach for the targeted transdermal delivery of antiarthritic drugs, providing sustained and controlled drug release that could significantly enhance therapeutic outcomes for arthritis patients. The study's findings highlight the potential of mesoporous silica nanoparticles in developing advanced drug delivery systems that improve drug solubility, stability, and targeted delivery.

Key words:
Mesoporous silica nanoparticles, antiarthritic gel, controlled release, transdermal delivery, Methotrexate, Tofacitinib Citrate