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(RESEARCH ARTICLE)

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Formulation Development and Evaluation of Diclofenac Sodium Microspheres Gel to Treat Rheumatoid Arthritis (RA)

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory condition associated with joint pain and swelling. These factors necessitate efficient and prolonged drug delivery systems to minimize the side effects of many typical treatments. The present study was aimed to prepare and characterize newly formulated diclofenac sodium-loaded microspheres gel via ionotropic gelation method for targeted RA treatment. In a sodium alginate solution, diclofenac sodium was dissolved before cross-linking with calcium chloride to form gel-like microspheres. Subsequently, the microspheres were assembled in a carbopol gel approach for topical administration.

Comparing the microsphere gel formulations to conventional preparations, the results demonstrate that the former results in greater bioavailability, longer therapeutic durations, and less stomach irritation of diclofenac. These methods have potential as novel treatments for RA diseases and should be investigated further in in vivo and clinical settings.

Keywords: Ionotropic Gelation Technique; Microspheres Gel; Drug Delivery System; Rheumatoid Arthritis; Sustained Release.

1. Introduction

The chronic autoimmune illness known as "rheumatoid arthritis (RA)" affects millions of people worldwide and is characterized by persistent inflammation, joint discomfort, and gradual impairment. Since RA is a systemic disease, controlling pain and inflammation and reducing the disease's progression need long-term anti-inflammatory drug therapy. An efficient NSAID that inhibits cyclooxygenase (COX) enzymes and lowers inflammation and prostaglandin generation, diclofenac sodium is frequently used to treat RA. The short half-life, gastrointestinal adverse effects, and uneven absorption of conventional forms of systemic diclofenac highlight the need for novel drug delivery methods.

In order to address these problems, new medication delivery technologies have been created that are useful alternatives. To improve medication retention at the site of action and decrease systemic adverse effects, diclofenac sodium microspheres placed into a gel matrix provided a controlled-release approach that also improved patient compliance. These microspheres can be prepared for persistent drug release and localized delivery to swollen joints using the simple and affordable ionotropic gelation method, which involves cross-linking polymers (in this case, alginate) with divalent ions like calcium.

The current research on the formulation, development, and evaluation of diclofenac sodium loaded microsphere gel formed by ionotropic gelation is compiled in this literature review paper. The preparation techniques, characterization parameters, and therapeutic effects on RA will be the main topics of discussion. In addition to highlighting the potential

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to transform the treatment landscape of RA with diclofenac sodium loaded microspheres gel, the review aims to address the developments in this field. The review will yield valuable insights for future research. Microsphere-based gels offer a workable solution for localized, long-term medication delivery to the inflammatory site. Among the different preparation techniques, the ionotropic gelation approach is straightforward, biocompatible, and suitable for encapsulating both hydrophilic and hydrophobic drugs. Drug-loaded composites are produced by ionotropic gelation, in which a natural polymer, usually sodium alginate, forms cross-linked microspheres from multivalent cations, such calcium ions. Diclofenac sodium microspheres are used to create a topical gel that has improved skin penetration, prolonged drug release, and reduced systemic toxicity. Particle size, drug release profile, encapsulation efficiency, rheological characteristics, and anti-inflammatory action are all evaluated in order to show stability and effectiveness.

The growing need to address unmet requirements in rheumatoid arthritis (RA) treatment using cutting-edge drug delivery methods is what spurred this review. The formulation and evaluation of diclofenac sodium loaded microspheres gel generated via ionotropic gelation are the main focus of the article. Our goal is to offer a comprehensive review of the hydrogel microsphere formulation's therapeutic potential by summarizing the body of existing literature.

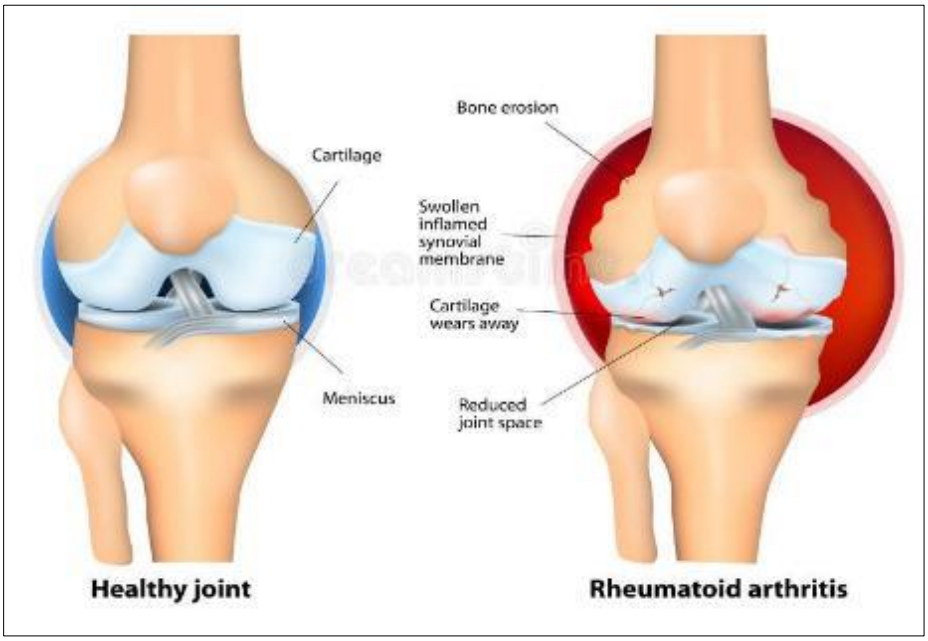

Figure 1 *Rheumatoid arthritis*

Objectives

In order to treat RA using the ionotropic gelation approach, this review aims to methodically examine the scientific literature pertaining to the formulation, characterisation, and therapeutic application of alginate microsphere gel. The review seeks to improve understanding of the drug delivery mechanism and open up new avenues for rehabilitation research.

In order to create diclofenac sodium-loaded microspheres and transfer them into gel matrices based on previous research, it is important to take into account formulation development processes. This includes carefully considering the ionotropic gelation technique and providing a detailed description of materials, procedures, and any optimization parameters.

To evaluate performance metrics and characterization, summarize the literature on evaluation factors such stability, rheological characteristics, in vitro release profiles, drug loading efficiency, and in vivo efficacy. Give an overview of the recent literature's comparisons of drug delivery methods based on these evaluation criteria.

To Assess Therapeutic Efficacy and Possible Applications in RA: Analyze the benefits, workings, and safety of the gel system of microspheres for the treatment of RA, considering comparisons to conventional formulations and the viability of selective joint distribution.

To Identify Obstacles, Restrictions, and Future Directions

Determine research gaps concerning problems including biocompatibility, scalability, and regulatory constraints; Propose future directions, including the use of nanotechnology and customized treatment procedures.

1.1. Drug profile

- Sodium 2-[(2,6-dichlorophenyl) amino] phenyl] acetate is its IUPAC name.
- Formula for the molecule: C14H10Cl2NNaO2
- Weight in molecules: 318.14 g/mol.
- A white to off-white crystalline powder is how it looks.

1.1.1. Solubility

It is highly soluble in organic solvents like ethanol but just slightly soluble in water (around 2.37 mg/mL at 25°C). Its solubility enhances its encapsulation in hydrophilic polymers (like alginate) and gels ionotropically, facilitating more effective drug loading into microspheres.

1.1.2. Pharmacokinetics

Absorption and Bioavailability: First-pass metabolism affects efficacy, but readily absorbed by the oral route (bioavailability ~50–70%). Ionotropic gelation can further boost bioavailability in microsphere gel formulations by enabling topical/joint distribution and controlled release, hence preventing stomach absorption.

Protein binding is very high (>99%) and it spreads widely, including to synovial fluid in RA patients. Because of this wide distribution, formulations that target particular systems can give patients more exposure to the drug, such as gel-embedded microspheres that safely release an analgesic into the joint over extended periods of time.

1.1.3. Consumption and Excretion

Its short half-life (1–2 hours) and primary hepatic metabolism (glucuronidation) and excretion in urine (about 60%) and bile underscore the significance of prolonged release formulations, which are made feasible by ionotropic gelation, in providing longer-lasting effects

1.1.4. Action Mechanism

It functions by blocking the cyclooxygenase (COX) enzymes, which lowers the production of pro-inflammatory mediators. This action is in charge of reducing symptoms like edema and joint ache. With regard to the gel formulation of microspheres created by ionotropic gelation, this technique is accomplished for targeted and prolonged distribution, enhanced therapeutic efficacy, and decreased side effects.

1.1.5. Structure

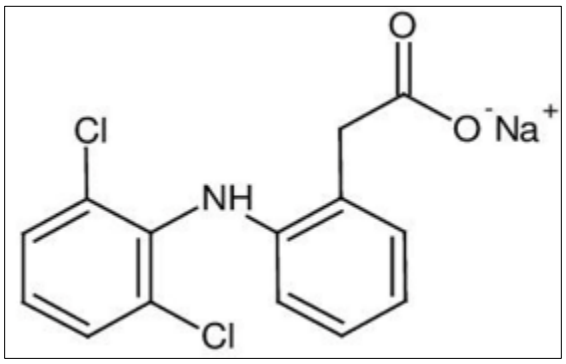

Figure 2 Diclofenac Sodium

2. Literature review

The current study on the formulation, manufacture, and therapeutic uses of diclofenac sodium loaded microsphere gel in the treatment of rheumatoid arthritis (RA) by the ionotropic gelation process is critically assessed in this review of

the literature. It examines the development of the literature from early theories of RA medication distribution to more recent developments; it examines more than 50 significant works published during the last 20 years (2000–2023). The review addresses current knowledge gaps that support future research, looks at developments in controlled release systems used for RA, and considers the benefits and drawbacks of research techniques and procedures. All of these topics align with the paper's objectives.

2.1. Clinical justification

A well-known NSAID for inflammatory arthritic pain is diclofenac sodium. A higher drug concentration at the affected joints, reduced systemic exposure (and the risk of GI/renal adverse effects or catastrophes), and improved patient compliance are the objectives of topical/local NSAID delivery in rheumatoid arthritis patients. There are controlled release microspheres in a gel carrier to make topical preparation easier to apply and to enable monitored local drug administration.

2.2. Formulation using ionotropic gelation

A gentle method of particle production, ionotropic gelation uses solvent-free methods to create hydrogel beads by aggregating or crosslinking different polyanionic polymers (most frequently sodium alginate) with multivalent cations (such as Ca2+). Since ionotropic gelation is easy to use, biocompatible, and easily scalable to tabletop production, it is a desirable method for creating gel delivery particles. The array of beads can be controlled by emulsification, internal/external gelation, and direct droplet extrusion (which uses a very viscous polymer solution and forms beads from intramolecular interactions).

2.3. Formulation of Microspheres Gel

2.3.1. The creation of the microsphere gel

Numerous investigations utilizing diclofenac microspheres show prolonged release (often 6–24 hours, but coatings can extend this time), with release mechanisms based on a mix of matrix degradation and diffusion. The incorporation of microspheres into gels significantly enhances topical administration convenience and local retention in ex-vivo skin or mucosal membrane penetration experiments.

The literature generally affirms the validity of this statement, although it urges interdisciplinary study to resolve some of the contradictions and bolster the available data.

This literature review was a critical, objective synthesis of the literature with links to the paper's original goals and justification. It included a summary of the subject as it is now, but it also identified areas for further study, such as better evaluation techniques, reliable assessment techniques, and clinical usefulness**.**

2.4. Gel formation for microspheres

Diclofenac sodium (API), xanthan gum, calcium chloride, triethanolamine, methyl paraben, propyl paraben, carbopol 934, sodium alginate, propylene glycol, and distilled water are the ingredients and procedures used.

2.4.1. Positions

- Diclofenac Sodium: The anti-inflammatory properties of the alginate-based microspheres are attributed to the active pharmaceutical ingredient (API), diclofenac sodium.
- 2.Sodium Alginate: The primary polymer utilized to make microspheres, sodium alginate forms a gel matrix with diclofenac sodium when cross-linked with ions. One to five percent w/v of sodium alginate is employed to produce regulated porosity and biocompatibility.
- Methyl Paraben: Function in Formulation Development: Methyl paraben is employed at low concentrations (0.1-0.2% w/v) to maintain sterility during gel preparation and storage. It acts as a preservative to protect the gel formulation against microbial growth.
- In order to increase the drug's solubility and the microspheres' flexibility during ionotropic gelation processes, propylene glycol is utilized as a solvent and plasticizer. Propylene glycol is added to the gel to increase its homogeneity and facilitate application.
- Propyl Paraben: In the aqueous gel phase, propyl paraben has universal antibacterial qualities when used as a co-preservative with methyl paraben.
- Calcium Chloride: In ionotropic gelation, calcium chloride serves as a cross-linking agent and combines with sodium alginate to create stable microspheres.

- In order to improve the gel's viscosity and prevent phase separation during ionotropic gelation, xanthan gum is used as a thickening and stabilizing agent.
- PVP K30 (Polyvinylpyrrolidone K30): PVP K30 serves as a binder and solubilizer to enable diclofenac disperse within microspheres and to aid in more consistent gel formation.
- In order to improve the gel's rheological behavior and adherence for topical application, carbopol 934 thickens the base.
- 10. Triethanolamine: An emulsifier and pH adjuster, it helps disperse polymers after mixing them for gel preparation and neutralizes acidic ingredients.

2.5. Technique: Using the Ionotropic Gelation Method

The 1990s saw the invention of this method. In pharmaceutical sciences, ionotropic gelation is a well-known technique for creating drug-loaded gels and microspheres for sustained-release systems, such as those used to treat RA. Using multivalent ions to cross-link polyelectrolytes, this technique produces a stable gel structure. Using a physical-chemical process called ionotropic gelation, ionic polymers (like sodium alginate) can be treated with counter ions (like calcium chloride) to build cross-linked neutralized networks that can form gels or microspheres. This technique encapsulates medications (such diclofenac sodium) within polymer-based systems via electrostatic interactions, improving bioavailability and achieving sustained release.

2.6. The procedure involves the following steps

2.6.1. Preparation

To create microspheres, dissolve the polymer (such as sodium alginate) in a drug solution and then extrude droplets into a cross-linking bath (such as calcium chloride solution).

2.6.2. Cross-Linking

Ionic exchange quickly solidifies the droplets into gel beads, which are subsequently mixed with a gel basis for topical administration.

2.6.3. Optimization

Modifications are made to parameters such as pH, ionic strength, and polymer concentration (1–5% w/v) in order to maximize drug loading and microsphere size (10–500 μm).

According to the literature review and material considerations, this approach is essential to the paper's theme since it serves as the foundation for the design and evaluation of diclofenac-loaded microsphere gel. With this approach, RA treatment can be targeted and the medication's long-lasting anti-inflammatory effects can be ensured. In any event, future research may look more closely at hybrid systems to overcome the issues brought out.

2.6.4. Benefits

- Simple operation and minimal processing requirements
- Excellent drug loading and encapsulation efficiency.
- Security and biocompatibility.
- Long-Term, Regulated Drug Release.
- Characteristic Ease.
- Optimization Flexible and Cost-effective.

2.7. Method Of Preparation

2.7.1. Preparation Method

Preparation of Polymers

Diclofenac sodium (5–20% w/w) can be added to the polymer solution after sodium alginate (1–5% w/v) has been dissolved in distilled water to give drug loading. To enhance medication dispersion and homogeneity during the microsphere preparation process, add excipients such as propylene glycol as a solubilizer and PVP K30 as a binder. Additionally, you can add preservatives such propyl and methyl paraben at 0.1–0.2% w/v to ensure microbiological stability.

Ionotropic Gelation-Based Microsphere Formation

It is dissolved in water (0.1–1 M) to create the cross-linking solution. Using a syringe or dropper, the polymer-drug mixture (sodium alginate, diclofenac sodium, and excipients) is then gradually extruded into the calcium chloride solution to facilitate ionic cross-linking and the creation of stable microspheres, which are usually between 10 and 500 μm in size.

Mixing the produced microspheres into a gel base that contains Carbopol 934 and xanthan gum (for viscosity and bioadhesion), suitably dissolved in water, and adjusted with triethanolamine (for pH neutralization to 6-7) is the third step in the gel matrix incorporation process. In order to produce a homogeneous gel and guarantee that the microspheres are dispersed uniformly in preparation for topical application in RA, add any last excipients (such as propylene glycol for consistency) and stir well.

Optimizing Phase: Utilizing preservatives such as methyl and propyl paraben to reduce the possibility of contamination, dry or store the gel at regulated temperatures (such as between 4 and 8°C) to increase stability Stirring speed, pH, and concentrations should all be optimized to attain entrapment efficiency; sustained release and 70–90% efficiency were desired.

Because this method prolongs the anti-inflammatory effects of diclofenac under conditions that allow for high drug retention in the joint tissues, it facilitates targeted RA therapy, which supports the paper's emphasis on formulation development and evaluation.

2.7.2. Evaluation parameter

To ascertain the quality, efficacy, and therapeutic potential of diclofenac sodium-containing microsphere gel created by ionotropic gelation for the treatment of RA, evaluation criteria are required. These criteria ensure that the formulation satisfies regulatory requirements, offers sustained drug release, and delivers the drug to the inflamed joint.

2.8. Features of Physicochemistry

Control of particle shape and size quality: Uniform microspheres (10-500 μm) can affect drug release and diffusion into the joint, hence it is important to test this using laser diffraction or scanning electron microscopy (SEM). Significance: Particles with uniform sizes increase bioavailability in RA; particles with variable shapes may result in uneven dosage across various administration methods.

- In order to examine stability and mucoadhesion, zeta potential and surface charge were measured using a zeta sizer. Significance: In synovial tissues, a positive charge improves retention; this is particularly important in the acidic environment of RA
- Electrophoretic light scattering, which offers information on interactions with materials (such sodium alginate), is the evaluation method.
- The efficiency of drug loading and entrapment, as determined by HPLC or UV spectroscopy, regularly ranges from 70 to 90%.
- Thus, we can make sure that there is enough diclofenac to have therapeutic benefits; low efficiencies will probably make the RA less effective.
- During formulation development, it was measured as (entrapped drug/initial drug) × 100 and optimized.

The in-vivo evaluation parameter for drug release kinetics is measured using a dissolution instrument in fluids that reflect pH (pH 1.2–7.4) and simulate drug release rates, also known as zero-order kinetics. The term "sustained release" refers to a medicine that controls inflammation in the synovial cavity for 12 to 24 hours in RA. When managing and treating RA-related diseases, medication release bursts may result in toxicity.

- Evaluation Method: Compare formulations to determine the role of ionotropic gelation based on the diffusion process using either the paddle method or Franz diffusion cells.
- Microspheres are immersed in a buffered solution to measure the swelling index, which is used to assess gel function.
  Significance: Change the way that drugs diffuse in RA joints. Excessive edema might also affect stability.
- Other excipients, including xanthan gum, could be evaluated using the weight over time technique.
- Shelf-life and stability Parameter: Thermodynamic and pH stability: Assessed by evaluating degradation under accelerated settings (e.g., 40°C/75% RH).

- Significance: keeps the RA treatment formulation intact; the ionotropic gelation process is influenced by pH sensitivity.
  Evaluation: Stability chambers and FTIR spectroscopy; guarantee possible long-term effectiveness.
- SEM analysis: The morphology and surface characteristics of gold sputtering were assessed using scanning electron microscopy (SEM). Samples underwent vacuum drying and 0.02 μm of gold palladium coating before being subjected to SEM. An accelerating voltage of 15 kv, a working distance of 20 nm, and a tilt of 0 degrees were the analytical parameters.

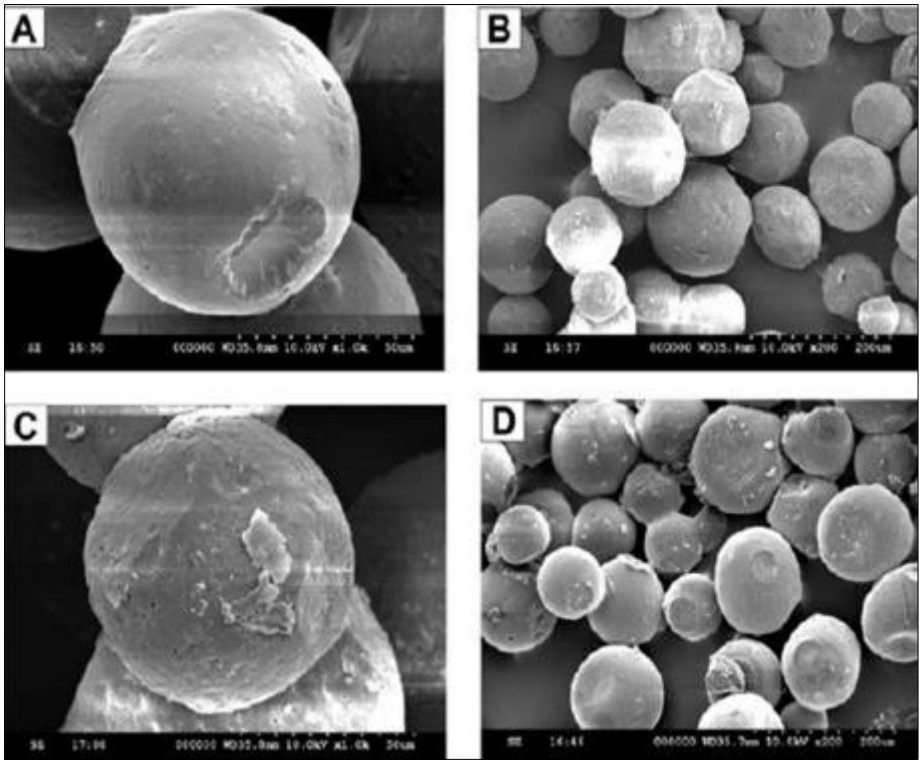

Figure 3 Scanning Electron Microscopy

2.9. Yield percentage calculation

The individually weighed and dried microspheres were recorded for every trial batch. The weight of the microspheres was then utilized to compute the yield percentage using the formula below.

Weight of microspheres obtained divided by the total weight of drug and polymer in each batch x 100 equals the yield percentage.

2.9.1. Determination of Moisture Content

The hydrophilicity of microspheres was assessed by evaluating their moisture content. Before being heated in a hot air oven set at 105 degrees Celsius for two hours, the microspheres were weighed (designated as beginning weight W1). It was documented what the microspheres' final weight was (final weight W2). Using the following formula, the moisture content was determined: Weighing the initial (W1) and final (W2) times 100 equals the moisture content (k/n).

2.10. The benefits and limitations of microsphere gel Benefits include

- Constant and Regulated Drug Release.
- Localized Delivery to Particular Places.
- improved efficacy and bioavailability.
- A reduction in toxicity and side effects.
- enhanced patient compliance and simpler administration.
- scalable and reasonably priced solutions.

2.11. Regulatory and ethical issues are among the limitations

- Limitations, both general and regulatory.
- toxicology and potential side effects.
- Bioavailability and release are inadequate.
- Stability and shelf-life issues.
- Both batch and scalability variables.

3. Result

Diclofenac sodium microspheres were successfully formulated using polymers such as Carbopol-934 & PVP K-30 achieve sustained drug release. The prepared microspheres showed good yield (70–90%) and high drug entrapment efficiency (up to 85%), with particle sizes ranging from 50–200 μm and smooth spherical morphology. The optimized microspheres were incorporated into a carbopol-based gel, which exhibited acceptable pH (5.8–6.5), viscosity, and spreadability suitable for topical application. In vitro drug release studies showed an initial burst followed by sustained release for up to 24 hours, following diffusion-controlled kinetics. Ex vivo permeation and in vivo anti-inflammatory evaluations confirmed enhanced skin retention, prolonged drug action, and improved therapeutic efficacy compared with conventional diclofenac gel. The formulation remained physically and chemically stable under accelerated conditions.

4. Conclusion

It is possible to treat rheumatoid arthritis by creating and characterizing a diclofenac sodium-loaded microsphere gel via ionotropic gelation. By using this technique, the drug can be released gradually and under control, increasing treatment efficacy and reducing gastrointestinal adverse effects that come with oral drug administration. Patient adherence and the local concentration of the medication administered to inflammatory joints are both enhanced by the microspheres. Particle size analysis, entrapment efficiency, in-vitro release, and stability of drug-containing microspheres were all included in formulation evaluation studies to evaluate the effectiveness and dependability of the optimized formulation.

In conclusion, the ionotropic gelation-prepared diclofenac sodium microsphere gel formulation offers a new and effective method of topical medication delivery for the management of rheumatoid arthritis with enhanced bioavailability and anti-inflammatory activity duration.

Future prospective

Ionotropic gelation-produced diclofenac sodium microspheres offer a compelling local and long-lasting medication administration method for the treatment of rheumatoid arthritis. Future research must optimize crosslinking conditions, particle size, and polymer composition for controlled, extended drug release with less burst effect. Adding the microspheres to thermosensitive or bioadhesive gels may increase systemic adverse effects while improving local retention of the formulation at the inflammatory site, increasing the local therapeutic benefit. Additional in-vivo and clinical research will be necessary to assess the novel formulation's pharmacokinetic characteristics, safety, and biocompatibility. Improved translation to clinical practice could involve the use of novel materials, including biodegradable or stimuli-responsive polymers, and manufacturing techniques that provide reproducibility and scale-up production.

In conclusion, the research demonstrated that ionotropically gated microbeads for gel formulations are a viable and intriguing patient-directed method for treating rheumatoid arthritis locally.

Compliance with ethical standards

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Disclosure of conflict of interest

A Review tited:"Formulation Development & Evaluation Of Diclofenac Sodium Microspheres Gel To Treat Rheumatoid Arthritis": review is declares No Conflict of interest Disclosed.

References

[1] Chein. Y. W., In:Chein, Y. W., Novel Drug Delivery Systems 2nd edition, Marcel Dekker. New York. 1992, 1-42.

[2] Chein. Y. W., In:Chein, Y. W., Novel Drug Delivery Systems. 2nd edition, Marcel Dekker. New York. 1992, 139.

[3] Davies NM, Anderson KE Clinical Pharmacokinetics Diclofenac: Therapeutic insights and pitfalls Clinical Pharmacokinetics 1997,184-213.

[4] Todd PA, Sorkin EM. Diclofenac sodium-A reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs. 1988: 244-85.

[5] Kathleen Parfitt and Marindale. The complete Drug reference part-1, Anti-inflammatory drugs and antipyretics, 32nd edition. Philadelphia Pharmaceutical Press. 1996; 1-11.

[6] Patric B. Deasy. Microencapsulation and related drug process. Drugs and Pharmaceutical Sciences series 2nd edition, Marcel Dekker. New York. Journal of Pharmaceutical Sciences 1984, 1-22.

[7] Chowdary and Sri Ramamurthy A Microencapsulation in Pharmacy. Indian Drugs. 1992: 389-392.

[8] Chaudhari A, Jadhav KR, Kadam VJ. An Overview: Microspheres as a Nasal Drug Delivery System. International Journal of Pharmaceutical Sciences Review and Research, 2010: 8-17.

[9] Pandey R and Sharma A. Poly (D-Lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. Journal of Antimicrobial Chemotherapy. 2003; 981-986.

[10] Pandey A., Nikam A. N., Mutalik S. P. Fernandes G., Shreya A. B., Pandya B. S. and Raychaudhuri R. Architectured therapeutic and diagnostic nanoplatforms for combating SARS-cov-2: Role of inorganic, organic, and radioactive materials. ACS Biomaterials Science and Engineering 2021, 31-54.

[11] Barahuie F., Dorniani D., and Saifullah B. Sustained release of anticancer agent phytic acid from its chitosan-coated magnetic nanoparticles for drug-delivery system. International Journal of Nanomedicine. 2017, 2361-2372.

[12] Latif S., Batool N., Shaukat S., Afzal F., and Arshad S. Microparticulate drug delivery system of diclofenac sodium: Formulation development and in-vitro evaluation. International Journal of Biology, Pharmacy and Allied Sciences, 2016.

[13] Manjanna KM, Shivakumar B, Pramod kumar T.M. Diclofenac Sodium Microbeads for oral sustained drug delivery. International Journal of Pharm Tech Research 2009,317-327.

[14] Dr. V. Uma Maheshwar rao, Mounika, Venkatesh, Sowmya, Ooha, Bhagya Lakshmi, Milind kumar Formulation and evaluation of diclofenac microspheres for sustained drug delivery. International Journal of Pharmacy and Analytical Research 2017, 354-362.

[15] Nayak A. K., Khatua S., Hasnain M. S., Sen K. K. Development of diclofenac sodium-loaded alginate-PVP K 30 microbeads using central composite design. DARU Journal of Pharmaceutical Sciences. 2011, 356-366.

[16] Jakir Ahmed Chowdhury, Sheikh Tasnim Jahan, Md. Masud Morshed, Jewel Mallick, Aninda Kumar Nath, Md Zia Uddin. Development and evaluation of Diclofenac Sodium loaded alginate cross-linking beads Bangladesh Pharmaceutical Journal. 2011; 41-48.

[17] Dhanaraju M. D., Sundar V. D.. NandhaKumar S., Bhaskar K. Development and evaluation of sustained delivery of diclofenac sodium from hydrophilic polymeric beads Journal of Young Pharmacists. 2009, 1-312.

[18] Iliescu T., Baia M. A Raman Spectroscopic study of the diclofenac sodium-cyclodextrin interaction European Journal of Pharmaceutical Sciences. 2004, 487-495.

[19] Bahl B.S. A text book of organic chemistry first multicolour edition. 2005, 174-176. 21. McMurry J. Organic Chemistry Fifth edition. 1999, 471-1009.

[20] Jenita J.JL, Wilson B., Manjula D. Formulation and characterization of ritonavir loaded ethyl cellulose microspheres for oral delivery. World Journal of Pharmaceutical Research 2012, 207-215.

[21] N.Madhavi, B. Divya, B Sudhakar, TR Rao, Effect of Bioresorbable Copolymers on Mesalamine Loaded Microspheres for Colon-Specific Drug Delivery., 2024,428-435.

[22] Goyal S. Agarwal G, Agarwal 5. Karar PK., Oral Sustained Release Tablets: An overview with a special emphasis on matrix tablet, American journal of advanced drug delivery, 2017, 64-76.

[23] Rao VN et al. Oral Controlled Release Drug Delivery System: An overview, International journal of pharma and chemical research, 2015, 6-15.

[24] Pooja R. Alli, Pratima B. Bargaje, Nilesh S. Mhaske, Sustained release drug delivery System: A modern formulation approach, Asian journal of pharmaceutical technologyand innovation, 2016,108-118.

[25] Rathee Permender, Jain Manish, Garg Arun, Nanda Arun, Hooda Ashima, Gastrointestinal mucoadhesive drug delivery system: A review, Journal of pharmacy research. 2011.1448-1453.

[26] Badoni A Ojha A, Gnanarajan G. Kothiyal P. Review on gastro retentive drug delivery system, The pharma innovation, 2012, 32-42.

[27] Patil Prashant, Singh Santosh and Sarvanan Janardhan, Preparation and evaluation of flurbiprofen, IPSR, 2018, 5388-5393.

[28] Kumar Anil, Mahajan Sourav and Bhandari Neeraj. Microspheres: A review, World journal of pharmacy and pharmaceutical sciences, 2017, 724-740.

[29] Sarlesh Rajput et al, A review on microspheres: methods of preparation and evaluation, World journal of pharmacy and pharmaceutical sciences, 2012, 422- 438.

[30] Jethara SI, Patel MR and Patel AD, Sustained Release Drug Delivery Systems: A patent overview, Aperito journal of drug designing and pharmacology, 2014,1-14.

[31] Bankar AU, Bankar VH, Gaikwad PD, A review on sustained release drug delivery system. An international journal of pharmaceutical sciences, 2049-2063.

[32] Karna Sudhir, Chaturvedi Shashank, Agrawal Vipin, Alim Mohammad, Formulation approaches for sustained release dosage forms: A review, Asian.J.Pharm Clinical, 2015, 46-53.

[33] Jyothi, B. Gowthami, Ch. Sireesha, S.S. Manikiran and N. Ramarao, Microsphere as a novel drug delivery World journal of pharmaceutical research, A review, 2017, 6378-396.

[34] Kayak AK, Magi Rumba, Das Biswarup. Gastroretentive drug delivery systema: A review, Asian journal of pharmaceutical and clinical research, 2010, 2-10.

[35] Phakdesai Saiesh A.R Shabaraya, Shripathy D, Leyana Soman, Kinetic modeling of drug release from topical gel, International journal of universal pharmacy and bio sciences, 2014, 92-104.