Current Rheumatology Research

Dhiman A, et al., Curr Rheumatol Res. 2025;5(1):27-30.

Commentary

Rethinking leflunomide in rheumatoid arthritis: Can innovative drug delivery approaches open new horizons?

Ashish Dhiman[1], Tejaswini Deshmukh[1], Kalpna Garkhal[1,*]

[1]Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research-Ahmedabad (NIPER-A), Palaj, Opposite Airforce Station, Gandhinagar-382355, Gujarat, India

*Author for correspondence: Email: Kalpna.garkhal@niperahm.res.in

Received date: September 15, 2025
Accepted date: November 10, 2025

Abstract

Leflunomide (LEF) is one of the most effective synthetic disease-modifying antirheumatic drugs (DMARD) which is widely prescribed for rheumatoid arthritis. But the safety issues of LEF makes its use compromised due to various side effects like hepatotoxicity, GIT disturbances, etc, and variable patient responses. The longer retention period of LEF in body is another issue which requires the washout period of almost 2 weeks using cholestyramine or activated charcoal for complete removal from the body, hence, contraindicated in pregnant women. However, the arrival of biologics and targeted synthetic DMARDs have diminished the use of LEF, although, this molecule has excellent anti-arthritic potential with maximum efficacy. Recent progress in innovative and novel drug delivery strategies for RA have yielded promising outcomes, opening new horizons for safer delivery of LEF to RA patients. Approaches like polymeric, transdermal, and lipid-based nano-cargoes have shown potential in increasing efficacy, solubility and minimizing the systemic toxicity. Furthermore, combination of LEF with other DMARDs and stimuli-triggered drug release techniques could lead to the development of integrated modalities for LEF delivery in RA patients. Here, in this commentary, we believe that if safety and efficacy issues with LEF is successfully addressed to a significant extent using smart and innovative drug delivery approaches, the underutilization can be reduced and can open new avenues for safer LEF delivery in RA patients.

Keywords: Rheumatoid arthritis, Leflunomide, Novel drug delivery systems, Arthritis, Disease-modifying antirheumatic drugs (DMARDs)

Introduction

Rheumatoid arthritis (RA) is a chronic and heterogeneous autoimmune disorder characterized by pain and inflammation of joints. More than 17.6 million people across the world had RA in 2020, indicating a sharp increase by 14.1% in cases since 1990 [1]. There are various treatments approved for the RA, which includes biologics and synthetic disease modifying anti-rheumatic drugs (DMARDs), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and sometimes analgesics as well to relieve pain and inflammation. Leflunomide, a synthetic and conventional DMARD, is a dihydroorotate dehydrogenase (DHODH) inhibitor causing alterations in immune responses and is a widely prescribed for the management of RA. Due to various challenges such as severe adverse effects like hepatotoxicity, gastrointestinal (GIT) disturbances, other factors such as varying clinical responses, encounter in LEF delivery to RA patients, it is underutilized [2]. The safety and efficacy issues of LEF can be resolved through innovative and novel drug delivery systems which can lead to as a safe, affordable, and easily available treatment.

Challenges in Current Dosage Form of LEF

Currently, LEF is available as 10, 20, 100 mg tablets under the brand name ARAVA® [3]. A variety

of challenges are faced during oral delivery of tablets mainly includes its side effects [2]. LEF have high albumin binding in blood plasma showing a high protein binding inside the body. The conversion of LEF to its active metabolite, teriflunomide *in vivo* and its deposition due to low blood circulation time in vital organs like liver causes toxicity in the body. Due to high drug plasma concentration after stoppage of dosage administration, a washout period for almost 2 weeks for complete removal of drug from the body is generally required. The complete removal of teriflunomide can take up to 2 years without accelerated elimination. The active metabolite, teriflunomide is removed through direct biliary elimination of untransformed drug along with renal excretion of metabolites. The removal of teriflunomide (metabolite of leflunomide) can be increased by administration of activated charcoal or cholestyramine. After this accelerated elimination, almost 23.1% was found more excreted through feces [4]. This longer retention of active metabolite in the body is the reason for teratogenicity of LEF, that's why it is contraindicated in pregnant females [5]. The current dosage form of LEF also counters a non-specific target producing off-target effects and high plasma protein binding. Therefore, the potential strategies are still to be explored for elimination of drug accumulation even after termination of drug administration and also for decreasing the high drug protein binding.

Additionally, a number of side effects such as hepatotoxicity, GIT disturbances, bone marrow suppression, weight loss and diabetes, hematological effects, skin rashes, ulcerative colitis, and others [2,6]. These side effects should be monitored using suitable assessment methodologies to get rid of safety issues that occur with LEF delivery. Patient counselling regarding proper administration and use of drug is still an important challenge which must be considered. Different clinical responses in different patient population are an issue which is a major concern. Since LEF has a very good oral bioavailability but still it is underutilized due to safety concerns, however, when other DMARDs are not effective, LEF is prescribed in such cases. Prolonged retention and slow onset of action is also a major reason for restricted use of LEF.

Innovative Approaches to Overcome LEF Underutilization

Several drug delivery approaches are underway to check their potential in minimizing the current underutilization of LEF due to delivery via conventional oral route which causes safety issues along with cost implications. Novel strategies such as use of nano-cargoes for LEF delivery, stimuli-responsive drug release, lipid-based drug delivery, photothermal and photodynamic therapy, and other types of drug delivery platforms have garnered attention in recent years [2]. The surface alteration/functionalization of nano-cargoes is another emerging strategy which can result in improved penetration for transdermal and topical delivery, controlled drug release, and tailored drug delivery. Additionally, topical and transdermal route are also explored to unravel their potential in safer delivery of LEF [7]. Hybrid and multifunctional systems are other carriers which have shown desired outcomes during last years in recent investigations. Hydrogel and injectable depot systems have also been instrumental in delivering the LEF to the inflamed sites with reduced side effect and increased efficacy [7–9]. Stimuli responsive delivery of LEF could also be gamechanger if its drug release can be controlled with certain internal or external stimulus to reduce dose and minimize side effects [10]. A rational drug combination of LEF with other DMARDs and drugs must be carried in a controlled-dosage regimens that can allow low dose with safer and more effective delivery [11]. The proper and personalized adjustment of titration period for maintenance and loading dose of LEF might also reveal a strategic adaptability in

Table 1. A summary of all innovative drug delivery approaches to overcome LEF underutilization.

Strategy / Platform	Advantages	Limitations / Disadvantages
Nanoparticles	Improved solubility, and bioavailability; controlled/ sustained release; decreased systemic toxicity	Potential cytotoxicity, scale-up challenges, cost, long-term safety still under evaluated
Stimuli-responsive delivery systems	On-demand, controlled release (triggered by pH, temperature, enzymes, etc.); lower side effects; personalized dosing	Complex design, regulatory hurdles, sometimes unpredictable *in vivo* responsiveness
Lipid-based carriers (e.g., SLNs, liposomes)	Enhanced skin permeability, sustained release, reduced dose, biocompatibility, non-toxic for topical delivery	Physical instability, costly lipid materials, scale-up difficulties
Hybrid/multifunctional systems	Combine multiple functions (e.g. targeting & imaging), improved efficacy, customizable	Expensive, may have larger regulatory barriers, challenging reproducibility
Photothermal/photodynamic systems	Site-specific activation, can enhance local efficacy, reduced off-target effects	Needs external energy source, risk of tissue overheating, technical complexity
Topical/transdermal delivery	Avoids first-pass metabolism; reduced GI and hepatic side effects; user convenience	Limited to drugs with suitable physicochemical properties, possible skin irritation
Injectable depot/hydrogel systems	Long acting, targeted to inflamed sites, fewer administrations, improved efficacy, lower systemic exposure	Injection discomfort, device-related complexity, potential depot clearance issues
Rational drug combinations	Lower doses of individual drugs, potential for synergistic efficacy, may reduce resistance	Higher complexity in dosing regimens, possible drug-drug interactions, regulatory issues
Personalized/titrated therapy	Tailored to patients, improved response, fewer adverse effects	Requires patient monitoring, may be less practical for large-scale, real-time adjustments
Patient-centered tools/ adherence strategies	Increased persistence, improved therapeutic outcomes, patient counselling	Implementation challenges, cost, need for education and digital tools

fluctuation of clinical responses that currently occur in patients [12]. Furthermore, a patient centered approach such as regular counselling and guidance before and after treatment must be followed, especially for females on LEF dosing and planning to conceive [13]. Since it is well established that LEF is prescribed when other DMARDs doesn't respond in the patient for RA, hence, such dose adherence tools and methodologies should be designed to ensure easy persistence of patients on LEF [2,13]. The personalized therapy could be another innovative remedy for designing the particular dose and time period of LEF therapy according to the state and symptoms of the RA patients [14]. Detailed research on innovative and novel solutions to find potential options for safer and efficacious delivery of LEF is required for RA patients.

Clinical Evidence

Numerous studies have been conducted to check the potential of various alternate drug delivery methods which can be instrumental in minimizing LEF underutilization. Shareef and coworkers developed LEF loaded transferosomes based hydrogel for the treatment of RA. *In vitro* evaluation of formulation depicted excellent hemocompatibility, high permeability, and sustained release behavior. *In vivo* studies in RA induced model demonstrated increased pharmacodynamic activity when assessed via quantification of attenuated behavioral responses, superior oxidative safety, and radiographic diagnosis [7]. Krishnan and coworkers formulated the LEF loaded nano-lipidic carrier for lymphatic targeting via chylomicron formation to reduce systemic side effects and increase bioavailability. *In vivo* test in Sprague-Dawley rats confirmed the antiarthritic potential of nano-lipidic carriers of LEF for almost 30 days with a significant reduction in inflammation when compared to standard drug. Intraduodenal administration of formulation showed the intestinal uptake of 40.34 µg/ml for LEF loaded nano-lipidic carriers as compared to 10.04 µg/ml of LEF drug solution. Histopathological studies confirmed the development of healthy cartilage in RA-induced rats [15]. Nanaki and colleagues designed chitosan nanoparticles (CS-NPs) for LEF delivery for preparation of aliphatic polyester-based skin patches. CS-NPs were incorporated into poly (l-lactic acid) (PLLA) or poly (lactic-*co*-glycolic acid) (PLGA) to prepare thin film skin patches for LEF delivery. A remarkable increase in LEF release rate was observed in CS-NPs after their incorporation in polymeric skin patches for drug delivery [16]. Zewail and her coworkers formulated nanostructured lipid carriers (NLCs) for LEF delivery coated with chondroitin sulphate (CHS) or chitosan (CS) to increase the therapeutic outcomes in RA. *In vivo* studies in RA induced rats improved inflammation of joints and showed marked reduction in liver toxicity after oral administration of LEF loaded CS/CHS coated NLCs suspension as compared to standard LEF drug solution. While highest plasma drug concentration and lowest tumor necrosis factor-alpha (TNF-α) were observed in CHC-NLCs. A synergistic effect is seen during joint healing with enhanced LEF concentration at inflamed joints [17]. Abbas and coworkers developed LEF-loaded emulsomes (EMLs) for intra-articular delivery in RA. EMLs were loaded with supramagnetic nanoparticles (SPIONs) to increase joint targeting. The drug release was achieved using the application of external magnetic field as a stimulus to SPIONs for enhanced localization of drug in joints [18]. A number of investigations are being conducted to find remedial alternatives for LEF delivery in RA to overcome its underutilization in RA, but clinical milestones to a significant status for greater efficacy and safety are yet to be established.

Future Directions

The future progress of LEF for treatment of RA lies in the development of patient-centered innovative and novel drug delivery strategies which can address problems in current dosage form. The integration of smart technologies such as stimuli-triggered drug release with novel approaches like nano-cargoes for LEF delivery could be exemplary in near future to unravel potential newer options for RA treatment with reduced side effects and raised efficacy. Nanocarriers such as nanoparticles, lipid-based formulation, etc. could resolve the issues of side effects associated with LEF, especially hepatotoxicity by opening new avenues for safer LEF in RA patients. Other unexplored routes of administration for LEF such as topical or transdermal should be researched using suitable robust RA induced animal models. Additionally, the newer drug combinations either LEF with some other DMARD for dual-drug delivery or multi-drug therapies should be investigated that can be helpful in unlocking newer solutions for RA treatment. The clinical translation of all developed technologies and strategies is yet another challenge in successful repositioning of LEF for safer and effective delivery.

Conclusion

Since LEF faces serious side effects and efficacy issues in current dosage form, finding the novel innovative formulation strategies for safe delivery of LEF can emerge as an optional therapy for RA over other DMARDs. The LEF delivery through topical or transdermal routes could also be a remedy to problems encountered in currently approved oral dosage form. Overall, it can be said that innovative and smart formulation strategies for safe and effective delivery of LEF through alternative routes of administration can reveal newer potential options.

Acknowledgements

Authors are thankful to NIPER-A library for providing necessary support in drafting this manuscript.

Conflicts of Interest

Authors declare no conflicts of interest.

References

1. Black RJ, Cross M, Haile LM, Culbreth GT, Steinmetz JD, Hagins H, et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2023 Oct 1;5(10):e594–610.
2. Dhiman A, Garkhal K. Leflunomide applicability in rheumatoid arthritis: drug delivery challenges and emerging formulation strategies. Drugs and Drug Candidates. 2025 Aug 1;4(3):36.
3. FDA, CDER. ARAVA® Tablets. Accessed on September 15, 2025. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020905s033lbl.pdf.
4. Aly L, Hemmer B, Korn T. From leflunomide to teriflunomide: drug development and immunosuppressive oral drugs in the treatment of multiple sclerosis. Current neuropharmacology. 2017 Aug 1;15(6):874–91.
5. Fukushima R, Kanamori S, Hirashiba M, Hishikawa A, Muranaka RI, Kaneto M, et al. Teratogenicity study of the dihydroorotate-dehydrogenase inhibitor and protein tyrosine kinase inhibitor Leflunomide in mice. Reproductive toxicology. 2007 Nov 1;24(3-4):310–6.

6. Osiri M, Shea B, Robinson V, Suarez-Almazor M, Strand V, Tugwell P, Wells G. Leflunomide for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2003 Jun;30(6):1182–90.

7. Shareef A, Ullah N, Sajid I, Mehmood A, Shah SU, Khan S, et al. Leflunomide loaded transferosomes based hydrogel against rheumatoid arthritis: In vitro and In vivo evaluation. Journal of Drug Delivery Science and Technology. 2025 Jul 1;109:106962.

8. Zewail M. Leflunomide nanocarriers: a new prospect of therapeutic applications. Journal of Microencapsulation. 2024 Nov 16;41(8):715–38.

9. Sanders S, Harisdangkul V. Leflunomide for the treatment of rheumatoid arthritis and autoimmunity. The American journal of the medical sciences. 2002 Apr 1;323(4):190–3.

10. Manisha, Pal P, Das P, Upadhyay VR. Stimuli-Responsive Drug Delivery Systems: From Concept to Clinical Translation. In: Next-Generation Drug Delivery Systems. New York, NY: Springer US; 2025. pp. 133–57.

11. Deng D, Zhou J, Li M, Li S, Tian L, Zou J, et al. Leflunomide monotherapy versus combination therapy with conventional synthetic disease-modifying antirheumatic drugs for rheumatoid arthritis: a retrospective study. Scientific reports. 2020 Jul 23;10(1):12339.

12. Johns Hopkins Arthritis Center. Rheumatoid Arthritis Treatment Options. Accessed on : September 12, 2025. Available online at: https://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis/ra-treatment/.

13. Nikose A, Patil S, Kadhe N, Aishwarya N, KADHE N. Understanding the Dual Challenge: Adverse Drug Reactions and Adherence in Rheumatoid Arthritis Treatment. Cureus. 2025 Jan 1;17(1):e76712.

14. Khokhar M, Dey S, Tomo S, Jaremko M, Emwas AH, Pandey RK. Unveiling novel drug targets and emerging therapies for rheumatoid arthritis: a comprehensive review. ACS pharmacology & translational science. 2024 May 28;7(6):1664–93.

15. Krishnan Y, Mukundan S, Akhil S, Gupta S, Viswanad V. Enhanced lymphatic uptake of leflunomide loaded nanolipid carrier via chylomicron formation for the treatment of rheumatoid arthritis. Advanced pharmaceutical bulletin. 2018 Jun 19;8(2):257–65.

16. Nanaki SG, Andrianidou S, Barmpalexis P, Christodoulou E, Bikiaris DN. Leflunomide Loaded Chitosan Nanoparticles for the Preparation of Aliphatic Polyester Based Skin Patches. Polymers. 2021 May 11;13(10):1539.

17. Zewail M, Nafee N, Helmy MW, Boraie N. Coated nanostructured lipid carriers targeting the joints–an effective and safe approach for the oral management of rheumatoid arthritis. International journal of pharmaceutics. 2019 Aug 15;567:118447.

18. Abbas H, Gad HA, El Sayed NS, Rashed LA, Khattab MA, Noor AO, et al. Development and evaluation of novel leflunomide SPION bioemulsomes for the intra-articular treatment of arthritis. Pharmaceutics. 2022 Sep 22;14(10):2005.