ORIGINAL ARTICLE

Formulation and Evaluation of Transdermal Patch of Leflunomide, Piroxicam, and Methotrexate for the Treatment of Rheumatoid Arthritis

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Abstract

Background: Rheumatoid Arthritis is a chronic autoimmune disease that requires prolonged therapeutic management. Conventional oral administration of anti-rheumatic drugs is often associated with gastrointestinal side effects, poor patient compliance, and fluctuating plasma drug concentrations. The present study was aimed at formulating and evaluating a combination transdermal patch containing Leflunomide, Piroxicam, and Methotrexate for controlled and effective treatment of rheumatoid arthritis. **Materials and Methods:** Transdermal patches were prepared using the solvent casting method with different ratios of hydrophilic polymer HPMC and hydrophobic polymer Ethyl Cellulose. Analytical methods including UV spectrophotometry and RP-HPLC were developed and validated for simultaneous estimation of the drugs. Preformulation studies such as organoleptic evaluation, solubility analysis, melting point determination, and compatibility studies were performed to assess drug purity and drug–excipient interactions. The formulated patches were evaluated for physicochemical parameters, mechanical properties, drug content uniformity, in-vitro drug diffusion, in-vivo pharmacokinetic performance, and stability under accelerated conditions. **Results and Discussion:** Compatibility studies confirmed the absence of significant drug–excipient interactions, indicating formulation stability. The prepared patches showed satisfactory thickness, folding endurance, moisture content, tensile strength, and uniform drug distribution. In-vitro diffusion studies demonstrated sustained and controlled drug release for up to 24 hours. Pharmacokinetic studies revealed enhanced bioavailability, prolonged therapeutic action, and reduced plasma concentration fluctuations compared to conventional oral therapy. Stability studies indicated that the optimized formulation remained stable under accelerated storage conditions. **Conclusion:** The developed combination transdermal patch of Leflunomide, Piroxicam, and Methotrexate demonstrated promising physicochemical characteristics, sustained drug release, improved bioavailability, and formulation stability. The study suggests that the transdermal delivery system may serve as an effective and patient-friendly alternative for long-term management of Rheumatoid Arthritis.

Key words: Combination therapy, leflunomide, methotrexate, piroxicam, rheumatoid arthritis, solvent casting, transdermal drug delivery system

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent inflammation of synovial joints and progressive joint destruction. Its pathophysiology is complex, involving a dysregulated immune response that targets the synovial membrane, ultimately leading to structural damage, deformity, and functional disability [Figure 1].[1,2] RA is distinct from degenerative conditions, such as osteoarthritis, as it primarily involves immune-mediated synovial inflammation rather than mechanical wear and tear. Epidemiological studies consistently show that RA affects approximately 0.5–1% of the global population, with considerable variation across geographical regions and ethnic groups (Smolen *et al*., 2016).[3,4] Women are disproportionately affected, with a female-to-male ratio of approximately 3:1, and peak disease

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onset typically occurs between 35 and 60 years of age, implicating hormonal and immunogenetic factors in disease susceptibility.[5,6]

Global burden and impact of RA

RA is recognized as one of the most prevalent chronic autoimmune diseases globally, contributing significantly to morbidity, disability, and socioeconomic burden. It affects approximately 1% of the world population, with higher prevalence among females and older adults, particularly between 35 and 60 years of age. RA is characterized by chronic inflammation of the synovial joints, resulting in pain, stiffness, joint deformity, and progressive functional disability.[7,8]

Transdermal drug delivery systems (TDDS)

Transdermal administration allows active chemicals to be absorbed into the circulation through the skin, resulting in systemic effects. One common approach to give medicine in this way is through transdermal patches. Ointments and patches are common methods of topical administration, allowing the drug to penetrate the skin and reach the circulation for a systemic effect. TDDSs are patches that are designed to administer a therapeutic dosage of medication through the skin. Effective administration of drugs with systemic effects requires consideration of the skin's unique morphological, biophysical, and physicochemical characteristics.[10]

Rationale for selecting leflunomide, piroxicam, and methotrexate (MTX)

MTX

MTX is the cornerstone disease-modifying anti-rheumatic drug (DMARD) used in RA. It inhibits dihydrofolate reductase, suppressing DNA synthesis and immune activation. Despite high efficacy, oral MTX commonly leads to GI disturbances, mucosal toxicity, and hepatotoxicity. Transdermal delivery offers potential to maintain therapeutic levels with fewer adverse effects.[11]

Leflunomide

Leflunomide inhibits dihydroorotate dehydrogenase, reducing pyrimidine synthesis and T-cell proliferation. Although effective, its long half-life and enterohepatic recycling cause severe hepatotoxicity and gastrointestinal (GI) effects. Transdermal administration can reduce hepatic exposure while retaining therapeutic benefits.

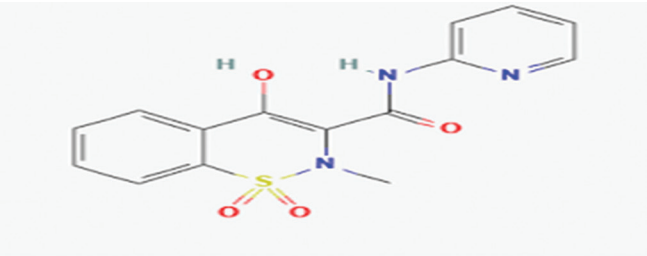
Piroxicam

Piroxicam is a potent non-steroidal anti-inflammatory drug (NSAID) offering analgesic and anti-inflammatory effects. Its oral use is limited by gastric ulceration, renal toxicity, and systemic side effects. Delivering piroxicam transdermally provides localized and systemic benefits with reduced GI complications.[12]

MATERIALS AND METHODS

The drugs used in this study were MTX, leflunomide, and piroxicam. Polymers, such as hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone were used as film-forming agents. Plasticizers and permeation enhancers, including propylene glycol and ethanol, were used to improve flexibility and drug permeation through the skin.

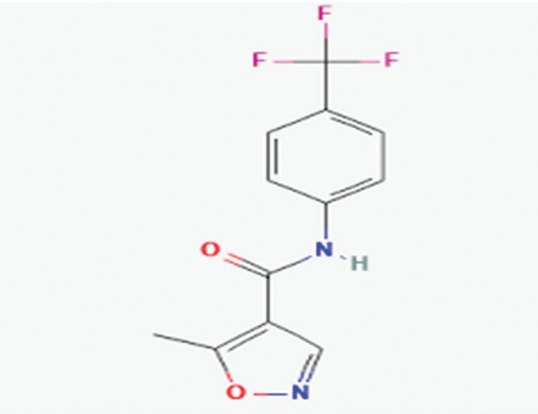
Drug profile of piroxicam



Structure of piroxicam

Piroxicam is a synthetic NSAID belonging to the oxicam class, extensively used in the management of chronic inflammatory and painful disorders, such as RA and osteoarthritis.

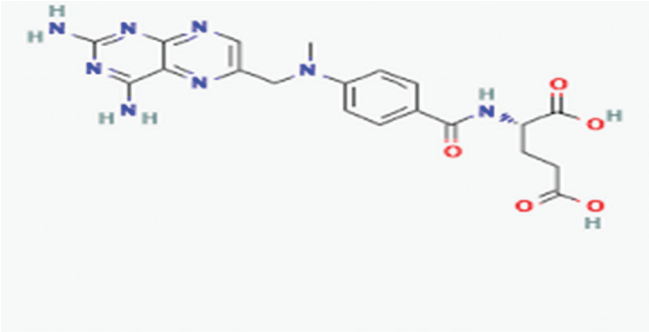
Drug profile of leflunomide



Structure of leflunomide

Leflunomide is a synthetic DMARD primarily prescribed for the management of RA and psoriatic arthritis.

Drug profile of MTX



Structure of MTX

MTX is a folic acid antagonist and one of the most widely used first-line DMARDs in the treatment of RA.

Drugs and excipients

- Active pharmaceutical ingredients: Leflunomide, piroxicam, and MTX were obtained as gift samples from a reputed pharmaceutical manufacturer and were of pharmaceutical grade.
- Polymers: HPMC E15, Ethyl cellulose (EC).
- Plasticizers: Polyethylene glycol 400, glycerol.
- Penetration enhancers: Oleic acid, propylene glycol.
- Solvents: Methanol, ethanol, distilled water.

All chemicals and reagents used were of analytical grade and were used without further purification.

Table 1: Composition of transdermal patch formulations

Ingredient	F1	F2	F3
Leflunomide (mg)	10	10	10
Piroxicam (mg)	5	5	5
Methotrexate (mg)	5	5	5
Hydroxypropyl methylcellulose (mg)	300	250	200
Ethyl cellulose (mg)	100	150	200
Polyethylene glycol 400 (mL)	0.5	0.5	0.5
Propylene glycol (mL)	0.5	0.5	0.5
Solvent	q.s	q.s	q.s

Table 2: Organoleptic properties of drugs

Drug	Color	Odor	Physical appearance
Leflunomide	White	Odorless	Crystalline powder
Piroxicam	White	Odorless	Crystalline powder
Methotrexate	White	Odorless	Crystalline powder

Methods

Preformulation studies

Preformulation studies were carried out to generate essential physicochemical data required for the successful development of transdermal patches. These studies focused on evaluating the identity, purity, solubility characteristics, thermal behavior, and compatibility of leflunomide, piroxicam, and MTX with selected excipients. The information obtained from pre-formulation studies provided a scientific basis for formulation design and ensured stability and performance of the final dosage form.

Organoleptic evaluation

The organoleptic properties of Leflunomide, Piroxicam, and MTX were evaluated visually to assess color, odor, and physical appearance. A small quantity of each drug was observed under normal lighting conditions to detect any discoloration, visible contamination, or physical irregularities. Organoleptic evaluation serves as a preliminary identification test and provides an initial indication of drug purity and stability.

Melting point determination

The melting point of each drug was determined using the capillary melting point method. A small quantity of the drug was packed into a thin-walled capillary tube sealed at one end and placed in a melting point apparatus. The temperature was gradually increased, and the temperature range at which the drug melted was recorded. The observed melting point range was compared with reported pharmacopoeial values to confirm

Table 3: Melting points of drugs

Drug	Reported melting point (°C)	Observed melting point (°C)
Leflunomide	165–166	162–165
Piroxicam	199–202	200–202
Methotrexate	195–197	196–197

Solubility of drugs in different solvents (mg/mL)

Drug	Water	Methanol	Ethanol	Phosphate buffer pH 7.4
Leflunomide	0.27	246	150	0.30
Piroxicam	0.04	50	35	0.05
Methotrexate	0.9	35	25	1.0

drug identity and purity. A narrow melting point range indicated the crystalline nature and purity of the drug substance.

Solubility studies

Solubility studies of leflunomide, piroxicam, and MTX were conducted using the equilibrium solubility method. Excess drug was added separately to distilled water, methanol, ethanol, and phosphate buffer pH 7.4. The mixtures were shaken continuously for 24 h at room temperature using a mechanical shaker to attain equilibrium. After equilibration, the solutions were filtered, suitably diluted, and analyzed spectrophotometrically.

Partition coefficient

The partition coefficient of each drug was determined using the shake flask method to assess its lipophilicity, an important parameter for transdermal drug delivery. Equal volumes of n-octanol and phosphate buffer, pH 7.4, were taken in a separating funnel, and a known quantity of drug was added. The mixture was shaken for 24 h and allowed to equilibrate. After phase separation, the aqueous layer was analyzed for drug content. The partition coefficient was calculated as the ratio of drug concentration in the organic phase to that in the aqueous phase.

Drug-excipients compatibility study Fourier transform infrared (FTIR)

Compatibility between drugs and excipients was evaluated using FTIR spectroscopy. Physical mixtures of each drug with individual excipients were prepared in suitable proportions and analyzed over a spectral range of 4000–400 cm^{-1} using the KBr pellet method. The spectra obtained were compared with that of the pure drug to identify any shifts, disappearance, or appearance of new peaks. The absence of significant spectral changes indicated chemical compatibility between the drug and formulation excipients.

Table 4: Partition coefficient of drugs

Drug	Partition coefficient (log P)
Leflunomide	2.5
Piroxicam	1.9
Methotrexate	0.8

Differential scanning calorimetry (DSC)

Thermal analysis of pure drugs and optimized formulations was performed using DSC. Accurately weighed samples (5–10 mg) were sealed in aluminum pans and heated over a temperature range of 30–300°C at a controlled heating rate under a nitrogen atmosphere. The thermograms obtained were analyzed for melting endotherms, peak shifts, or disappearance of characteristic transitions. DSC analysis was employed to study drug crystallinity and possible drug–polymer interactions.

Preparation of transdermal patches

Transdermal patches containing Leflunomide, Piroxicam, and MTX were prepared by the solvent casting method. The required quantities of HPMC and EC were dissolved in a suitable solvent system with continuous stirring to obtain a homogeneous polymeric solution. Plasticizers and penetration enhancers were added, followed by the incorporation of drugs under constant stirring to ensure uniform distribution. The resulting solution was poured into glass molds and allowed to dry at room temperature. After complete drying, the films were carefully removed, cut into uniform sizes, and stored in a desiccator until further evaluation (Table 1).

Thickness of transdermal patches

The thickness of the prepared transdermal patches was determined to assess the uniformity of film formation and to ensure consistency in drug distribution and release characteristics across the patch surface. Thickness was measured using a calibrated digital Vernier caliper with a least count of 0.01 mm. Measurements were taken at three to six different points on each patch, including the center and peripheral areas, to capture possible variations arising from casting and drying processes.

Folding endurance

Folding endurance was evaluated to determine the mechanical flexibility and durability of the transdermal patches under repeated stress conditions. This parameter reflects the ability of the patch to withstand repeated folding and handling during application, storage, and use without

Table 5: Differential scanning calorimetry thermogram readings

Sample	Endothermic peak (°C)	Enthalpy (ΔH, J/g)	Interpretation
Leflunomide (pure)	165.8	74.3	Crystalline drug
Hydroxypropyl methylcellulose	Broad peak	-	Amorphous polymer
Ethyl cellulose	Broad peak	-	Amorphous polymer
Optimized formulation	158.2 (broadened)	42.5	Drug molecularly dispersed

cracking or breaking. For the test, patches were cut into uniform dimensions to ensure consistency across samples. Each patch was repeatedly folded manually at the same point, either lengthwise or crosswise, depending on the orientation of the film, until visible cracks appeared or the patch broke completely. The number of folds required to cause failure was recorded as the folding endurance value for that patch.

Tensile strength

For tensile strength determination, rectangular strips of uniform dimensions were cut from the prepared patches. Each strip was clamped between two grips of a tensile strength testing apparatus or a modified pulley-based system. One end of the strip was fixed, while a progressively increasing load was applied to the other end until the patch broke. The force required to break the film and the elongation at the breaking point were recorded.

Drug content uniformity

For drug content analysis, a defined area of the transdermal patch was accurately cut and weighed. The patch sample was placed in a stoppered volumetric flask containing a suitable solvent system capable of completely extracting the drug from the polymer matrix. The flask was kept on a mechanical shaker for a pre-determined duration to ensure complete drug dissolution. The resulting solution was then filtered to remove polymeric debris and diluted appropriately.

The drug concentration in the filtrate was determined using a validated UV-visible spectrophotometric method at the pre-determined λ_{max} of the drug.

In vitro drug release studies

In vitro drug release studies were carried out to evaluate the release behavior and kinetics of drug diffusion from the transdermal patches.

The Franz diffusion cell assembly consisted of a donor compartment and a receptor compartment separated by a dialysis membrane. Before the experiment, the dialysis membrane was soaked in phosphate buffer, pH 7.4, to ensure hydration and remove preservatives. The receptor compartment was filled with phosphate buffer pH 7.4, selected to simulate physiological conditions, and maintained at 32 ± 0.5°C using a circulating water bath to mimic skin surface temperature.

RESULTS AND DISCUSSIONS

Preformulation studies

Organoleptic evaluation

The organoleptic evaluation of Leflunomide, Piroxicam, and MTX revealed that all three drugs were white crystalline powders, odorless, and free from visible contamination or irregularities (Table 2).

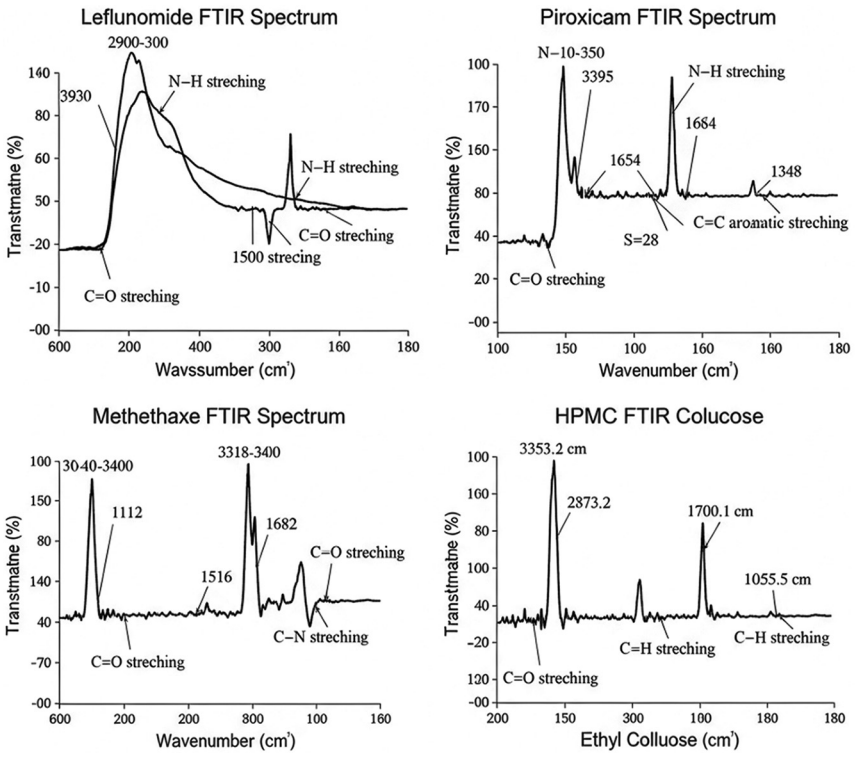


Table 6: Calibration curve parameters (ultraviolet method)

Drug	λ_{max} (nm)	Linearity range (µg/mL)	Regression equation	R^2
Leflunomide	276	2–12	y=0.083x+0.012	0.998
Piroxicam	334	2–12	y=0.091x+0.015	0.997
Methotrexate	303	2–12	y=0.076x+0.010	0.996

Melting point determination

The melting point of the drug was found (Table 3).

Solubility of Drugs

Solubility studies revealed significant differences among the three drugs. (Table 4).

Partition Coefficient of Drugs

The partition coefficient (log P) of the sample was determined (Table 5). DSC Thermogram was determined Ttable 6.

FTIR spectroscopy

FTIR spectroscopy was carried out to identify the characteristic functional groups of all three drugs, namely, leflunomide, piroxicam, and MTX, as well as polymers and excipients used in the formulation. FTIR analysis also aimed to assess possible drug-excipient interactions. Spectra were recorded in the range of 4000–400 cm^{-1} using the KBr pellet method.

Ultraviolet (UV)-visible spectrophotometric method

UV spectrophotometric methods were developed for the individual and simultaneous estimation of leflunomide, piroxicam, and MTX.

Evaluation of prepared transdermal patches

Physical appearance

All prepared transdermal patches were observed to be smooth, uniform, flexible, and free from visible defects, such as air bubbles, cracks, surface irregularities, or drug crystallization.

Thickness

The thickness of the prepared transdermal patches was measured using a digital micrometer at three different points, and the mean ± standard deviation values were calculated.

Thickness of transdermal patches (mean±standard deviation, mm)

Formulation	Thickness (mm)
F1	0.35±0.02
F2	0.38±0.03
F3	0.40±0.01

Folding endurance

Folding endurance was determined to evaluate the mechanical durability and flexibility of the patches.

Folding endurance of transdermal patches

Formulation	Folding endurance (No. of folds)
F1	120±5
F2	115±6
F3	110±4

Tensile strength of transdermal patches

Formulation	Tensile strength (MPa)	Elongation at break (%)
F1	2.8±0.12	18.5±0.8
F2	3.0±0.15	17.2±1.0
F3	3.2±0.10	16.8±0.7

Drug content of transdermal patches (% of theoretical)

Formulation	Leflunomide	Piroxicam	Methotrexate
F1	98.5±0.5	97.8±0.6	96.9±0.7
F2	97.6±0.4	98.2±0.5	97.1±0.5
F3	96.8±0.6	97.5±0.7	96.3±0.6

In vitro drug release

Cumulative drug release (%) from patches (leflunomide)

Time (h)	F1	F2	F3
1	12.5±0.3	10.8±0.5	9.2±0.4
4	35.2±0.5	32.1±0.6	30.4±0.5
8	58.4±0.6	55.2±0.7	52.8±0.6
12	72.1±0.7	68.5±0.8	65.2±0.7
24	85.7±0.8	82.3±0.9	79.1±0.8

Swelling index (%) of patches

Formulation	Swelling index (%)
F1	24.3±0.5
F2	23.1±0.4
F3	22.5±0.6

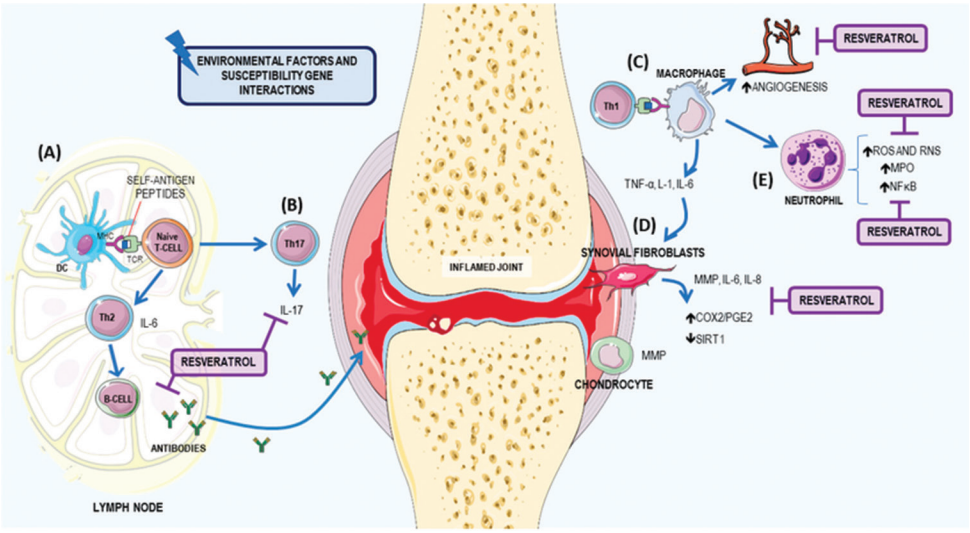


Figure 1: Pathophysiological mechanisms in rheumatoid arthritis.[9]

In vitro diffusion analysis

In vitro diffusion profile of drugs from transdermal patches			
Time (h)	**Leflunomide (%)**	**Piroxicam (%)**	**Methotrexate (%)**
	F1	**F2**	**F3**
4	28.6±0.7	25.1±0.6	22.3±0.5
8	51.8±0.9	48.2±0.8	44.6±0.7
12	68.9±1.0	64.5±0.9	60.8±0.8
24	85.7±0.8	82.3±0.9	79.1±0.8

Stability studies of TDDS

Stability studies were carried out as per the International Council for Harmonization (ICH) guidelines under accelerated conditions for 3 months. All formulations remained physically stable with no significant changes in drug content or release behavior.

Stability study results			
Parameter	**F1 (Initial/3 months)**	**F2 (Initial/3 months)**	**F3 (Initial/3 months)**
Physical appearance	No change	No change	No change
Drug content (%)	98.5/97.9	97.6/96.8	96.8/95.9
Release at 24 h (%)	85.7/84.9	82.3/81.6	79.1/78.2

CONCLUSION

The drug release from the formulated transdermal patches followed diffusion-controlled kinetics, which is characteristic of matrix-based transdermal systems and indicates predictable and controlled drug release. *In vivo* studies confirmed the effectiveness of the developed transdermal patches by showing prolonged therapeutic action and reduced peak-to-trough plasma fluctuations compared to oral administration. Pharmacokinetic studies revealed increased half-life, delayed Tmax, reduced Cmax, and increased Area Under Curve (AUC), indicating sustained drug absorption and improved bioavailability. These results suggest that transdermal delivery can maintain effective plasma drug levels for a longer duration while minimizing dose-related side effects, which is beneficial in chronic diseases, such as RA.

Stability studies performed according to ICH guidelines demonstrated that the optimized transdermal patches were physically and chemically stable, with no significant changes in appearance, drug content, or release profile.

Overall, the study successfully demonstrated that a combination transdermal patch of Leflunomide, Piroxicam, and MTX provides controlled drug delivery, improved pharmacokinetics, reduced dosing frequency, and better patient compliance. Thus, the developed TDDS represents a promising alternative to conventional oral therapy for the management of RA.

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