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FORMULATION AND EVALUATION OF METHOTREXATE AND RUTIN TOPICAL HYDROGEL FOR TREATMENT OF PSORIASIS

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Abstract:

Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by hyperproliferation of keratinocytes, erythematous plaques, and scaling, significantly affecting the quality of life of patients. Conventional systemic therapies such as methotrexate are effective but are associated with serious adverse effects, including hepatotoxicity and gastrointestinal complications, which limit long-term use. The present study aimed to formulate and evaluate a topical hydrogel containing Methotrexate and Rutin for the effective management of psoriasis. Methotrexate acts by inhibiting keratinocyte proliferation and suppressing inflammatory responses, while Rutin, a naturally occurring flavonoid, exhibits potent antioxidant and anti-inflammatory activities that may enhance therapeutic efficacy and reduce drug-induced toxicity.The hydrogel formulation was developed using suitable hydrophilic polymers to achieve optimal viscosity, spreadability, drug release, and patient acceptability. The prepared formulations were evaluated for physicochemical characteristics including appearance, pH, homogeneity, viscosity, spreadability, drug content uniformity, and in vitro drug release profile. The combination hydrogel demonstrated satisfactory formulation characteristics with sustained drug release and improved skin retention properties. The synergistic action of Methotrexate and Rutin provided enhanced anti-inflammatory and antioxidant effects, potentially improving therapeutic outcomes while minimizing systemic adverse effects.

The study concludes that Methotrexate-Rutin topical hydrogel represents a promising, safe, and effective alternative to conventional psoriasis therapies and may offer improved patient compliance and targeted drug delivery for long-term disease management.

Keywords: Psoriasis, Methotrexate, Rutin, Topical Hydrogel, Controlled Drug Delivery

1. INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disease that primarily affects the skin but is now recognized as a systemic autoimmune disorder. It affects approximately **2–3% of the global population** and is characterized by rapid proliferation of epidermal keratinocytes, resulting in **erythematous plaques covered with silvery-white scales**. The disease develops through a complex interaction of **genetic predisposition, immune dysregulation, and environmental triggers**.

The pathogenesis of psoriasis is mainly driven by **T-helper (Th1 and Th17) lymphocytes**, which release inflammatory cytokines such as **Tumor Necrosis Factor-α (TNF-α), Interleukin-17 (IL-17), and Interleukin-23 (IL-23)**. These cytokines accelerate keratinocyte turnover from the normal **28–30 days to only 3–4 days**, leading to hyperkeratosis and plaque formation. This understanding has facilitated the development of targeted biological therapies that interrupt these inflammatory pathways.

Psoriasis presents in several clinical forms, with **Plaque Psoriasis (Psoriasis Vulgaris)** accounting for **80–90% of cases**. Other variants include **Guttate Psoriasis**, **Inverse Psoriasis**, **Pustular Psoriasis**, and **Erythrodermic Psoriasis**, the latter being a severe medical emergency. Beyond skin involvement, psoriasis is associated with systemic comorbidities such as **Psoriatic Arthritis, obesity, diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular disease**, significantly affecting patients' quality of life and psychological well-being.

Conventional treatment strategies include **topical therapies, phototherapy, and systemic medications**. Topical corticosteroids, vitamin D analogues, and retinoids are commonly used for mild disease, whereas **Methotrexate (MTX)**, cyclosporine, and biologics are preferred for moderate-to-severe cases. Despite its effectiveness, MTX therapy is limited by adverse effects including **hepatotoxicity, gastrointestinal disturbances, and bone marrow suppression**.

Methotrexate acts as a folate antagonist by inhibiting **dihydrofolate reductase**, thereby reducing keratinocyte proliferation and suppressing inflammatory immune responses. **Rutin**, a naturally occurring flavonoid present in citrus fruits and buckwheat, possesses significant **antioxidant and anti-inflammatory properties** and has demonstrated potential in reducing oxidative stress and inflammatory cytokine production.

The combination of **Methotrexate and Rutin** offers a promising synergistic approach for psoriasis management. While MTX suppresses immune activation and cell proliferation, Rutin may enhance anti-inflammatory activity and protect against MTX-induced organ toxicity, particularly in the liver and gastrointestinal tract.

Recently, **topical hydrogel systems** have emerged as advanced drug delivery platforms for psoriasis treatment. Hydrogels provide **improved skin penetration, sustained drug release, enhanced patient compliance, and reduced systemic toxicity**. A **Methotrexate-Rutin topical hydrogel** combines the therapeutic efficacy of both agents with localized delivery, potentially improving treatment outcomes while minimizing adverse effects associated with conventional systemic therapy. This novel approach represents a promising strategy for safer and more effective management of psoriasis

2. AIM & OBJECTIVES

AIM

To formulate and evaluate Methotrexate and Rutin topical hydrogel for treatment of psoriasis

OBJECTIVES

- To develop a homogeneous topical hydrogel formulation of Methotrexate and Rutin using appropriate excipients.
- To evaluate the pH, viscosity, spreadability, and uniformity of drug content of the optimized topical hydrogel formulation.
- To study the *in-vitro* drug release and *in-vitro* kinetic studies for formulated topical hydrogel.
- To study the Thermostability of the formulated topical hydrogel to ensure stability.

3. PLAN OF WORK

a. Pre formulation studies:

- Determination of Melting point
- Solubility Study
- Calibration study of Methotrexate

- Compatibility study using FTIR

b. Formulation of topical hydrogel

c. Evaluation of topical hydrogel

- Visual appearance
- Determination of pH
- Spreadability
- Drug content uniformity
- Determination of Viscosity
- *In-vitro* study of drug release
- *In-vitro* kinetic studies
- Thermostability study

4. MATERIALS AND METHODOLOGY

MATERIALS AND METHODOLOGY

Materials

Methotrexate and Rutin were selected as the active pharmaceutical ingredients for the preparation of the topical hydrogel. HPMC K4M and Poloxamer 407 were used as gelling and thermosensitive polymers, while Hyaluronic acid was incorporated to improve hydration, spreadability, and skin compatibility. Sodium chloride served as an isotonicity-adjusting agent and sodium benzoate was used as a preservative. DMSO acted as a solubilizing agent, and phosphate buffer solution (pH 6.8) was used during analytical and drug release studies.

The instruments used in the study included a melting point apparatus, digital balance, FTIR spectrophotometer, magnetic stirrer, digital pH meter, Brookfield viscometer, dissolution test apparatus, UV-Visible spectrophotometer, and standard laboratory glassware.

Table: 1

S.NO	Ingredients	Suppliers
1	Melting point apparatus	SESW Melting point apparatus
2	Digital balance	Labindia.
3	FTIR Spectrophotometer	Shimadzu, Japan. (Model: FTIR- 84005)

4	Magnetic stirrer	Plastocrafts
5	pH meter	Systronics
6	Brookfield viscometer	AMETEK Brookfield
7	Dissolution test apparatus	Labindia. (Model: Disso 2000)
8	UV-Visible Spectrophotometer	Shimadzu Scientific Instruments. (Model: BL-220H)
9	Glass wares	Sigma Scientific Glass Pvt. Ltd, Chennai.

Methodology

Preformulation Studies

Preformulation studies were performed to determine the physicochemical characteristics of Methotrexate and its suitability for formulation development.

The melting point of Methotrexate was determined using the capillary method with a melting point apparatus. Solubility studies were carried out in distilled water, ethanol, phosphate buffer pH 6.8, and DMSO to identify a suitable solvent system for formulation development.

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Methotrexate (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Rutin (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K4M (mg)	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5
Hyaluronic acid (mg)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Poloxamer 407 (mg)	1	1	1	1	1	1	1	1
Sodium chloride(mg)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Sodium Benzoate (mg)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
DMSO (ml) (% v/v)	5	5	5	5	5	5	5	5
Distilled Water (ml)	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml	Up to 100ml

Table: 2

A calibration curve of Methotrexate was prepared by dissolving the drug in DMSO and preparing serial dilutions of different concentrations. The absorbance of each solution was measured using a UV-Visible spectrophotometer at 302 nm, and a standard calibration curve was constructed.

Drug-excipient compatibility studies were performed using Fourier Transform Infrared Spectroscopy (FTIR) to identify any possible chemical interactions between Methotrexate, Rutin, and excipients such as HPMC K4M and Hyaluronic acid. The spectra obtained for pure drugs and physical mixtures were compared for any changes in characteristic peaks.

Formulation of Methotrexate-Rutin Topical Hydrogel

The topical hydrogel was prepared by dispersing HPMC K4M in hot distilled water under continuous stirring to obtain a smooth viscous gel base. Poloxamer 407 was dissolved separately in cold distilled water and mixed with the HPMC dispersion to produce a uniform polymeric matrix. Hyaluronic acid was subsequently incorporated to improve moisture retention and skin compatibility.

Methotrexate and Rutin were dissolved in a small quantity of DMSO and incorporated into the polymer mixture with continuous stirring to ensure uniform distribution of the drugs. Sodium chloride and sodium benzoate were added to maintain isotonicity and stability of the formulation. The final volume was adjusted using distilled water to obtain a homogeneous topical hydrogel, which was stored under refrigerated conditions until further evaluation.

Several formulations were prepared by varying the concentration of HPMC K4M while maintaining constant concentrations of Methotrexate, Rutin, Hyaluronic acid, Poloxamer 407, sodium chloride, sodium benzoate, and DMSO.

Evaluation of Topical Hydrogel

The prepared hydrogels were evaluated for their physical appearance, including colour, clarity, homogeneity, and absence of particulate matter.

The pH of each formulation was measured using a calibrated digital pH meter to ensure compatibility with skin pH and minimize irritation upon application.

Spreadability was determined using the glass slide method, where the time required for two glass slides to separate under a specified load was measured. Improved spreadability was indicated by a shorter separation time.

Drug content uniformity was assessed by dissolving a known quantity of hydrogel in phosphate buffer solution and analyzing the drug concentration using UV spectrophotometry to ensure uniform distribution of Methotrexate and Rutin within the formulation.

Viscosity measurements were performed using a Brookfield viscometer at controlled temperature conditions to evaluate the rheological properties of the hydrogel and its suitability for topical application.

In-vitro drug release studies were carried out using a Franz diffusion cell containing phosphate buffer pH 6.8 as the receptor medium. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically to determine the release profile of both drugs.

The release data obtained were fitted into various kinetic models including Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models to determine the mechanism of drug release from the hydrogel matrix.

Stability studies were performed by storing the optimized formulation under refrigerated conditions for thirty days and evaluating it periodically for changes in appearance, pH, drug content, and drug release characteristics.

The developed Methotrexate-Rutin topical hydrogel was designed to provide controlled drug release, improved skin retention, enhanced therapeutic efficacy, and reduced systemic toxicity for the management of psoriasis.

5. RESULTS AND DISCUSSIONS

Preformulation Studies

The melting point of Methotrexate was determined using the capillary method and was found to be 195°C, which closely matched the reported literature value of 190–195°C, confirming the purity and thermal stability of the drug.

Solubility studies revealed that Methotrexate was poorly soluble in distilled water and only partially soluble in ethanol and phosphate buffer pH 6.8, whereas it exhibited excellent solubility in DMSO. Due to its superior solubilizing ability and permeation-enhancing property, DMSO was selected as the solvent for formulation development.

The calibration curve of Methotrexate was established using UV-Visible spectrophotometry at 302 nm and showed excellent linearity over the selected concentration range with a correlation coefficient ($R^2 = 0.9991$). The results confirmed the accuracy and reproducibility of the analytical method for quantitative estimation of Methotrexate in hydrogel formulations.

Solvent	Solubility
Distilled water	Poorly soluble
Ethanol	Partially soluble
Phosphate buffer 6.8	Partially soluble
DMSO	Soluble

Table:3

FTIR studies were performed to evaluate the compatibility between Methotrexate, Rutin, and the selected excipients. Characteristic peaks corresponding to functional groups of both drugs were retained in the physical mixtures without any significant shifts or disappearance of peaks, indicating the absence of chemical interaction and confirming compatibility among formulation components.

Concentration	Mean Absorbance (n=15)
0	0
1	0.0448
2	0.0860
3	0.1272
4	0.1684
5	0.2096
6	0.2508
7	0.2920
8	0.3332
9	0.3744
10	0.4156
11	0.4568
12	0.4980
13	0.5392
14	0.5804

TABLE:4

Formulation of Topical Hydrogel

Methotrexate-Rutin topical hydrogels were successfully prepared using HPMC K4M, Poloxamer 407, and Hyaluronic acid as the polymeric matrix. The formulations appeared homogeneous and stable without evidence of precipitation or phase separation during refrigerated storage. Hyaluronic acid contributed to improved hydration and spreadability, while sodium chloride and sodium benzoate enhanced isotonicity and formulation stability.

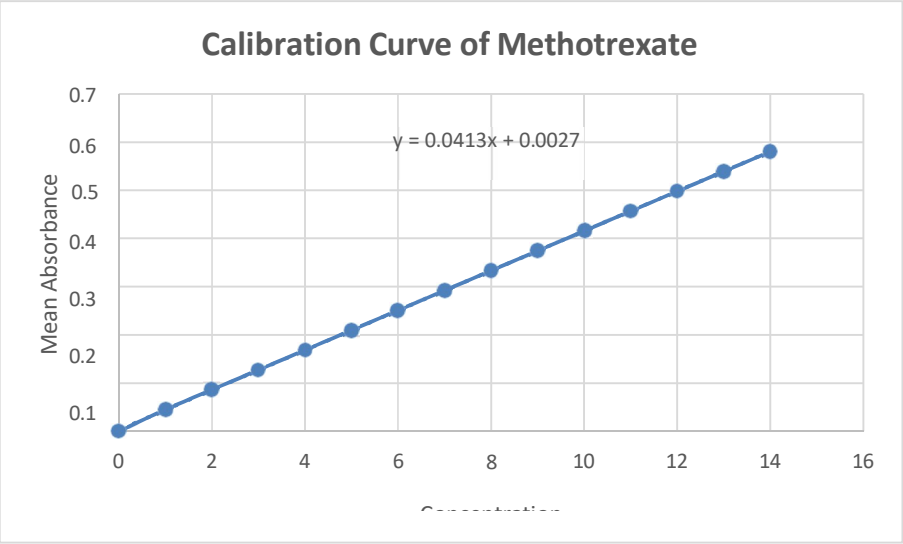

Figure.1: Calibration curve of Methotrexate

Evaluation of Topical Hydrogel

The visual appearance of the formulations varied depending on polymer concentration. Lower polymer concentrations produced liquid or low-viscosity gels, whereas higher concentrations resulted in thick translucent gels. Among all formulations, F5 exhibited a smooth, homogeneous, and translucent appearance with desirable consistency for topical application.

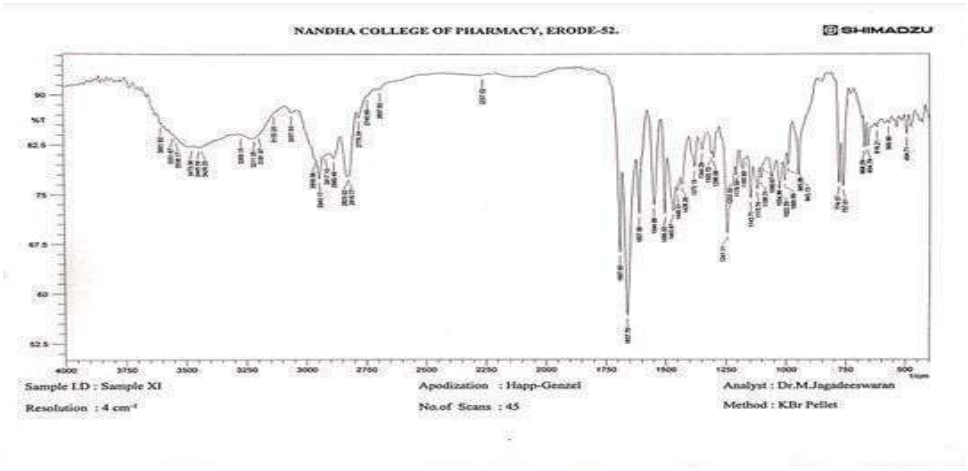

Figure.2 FTIR of Rutin

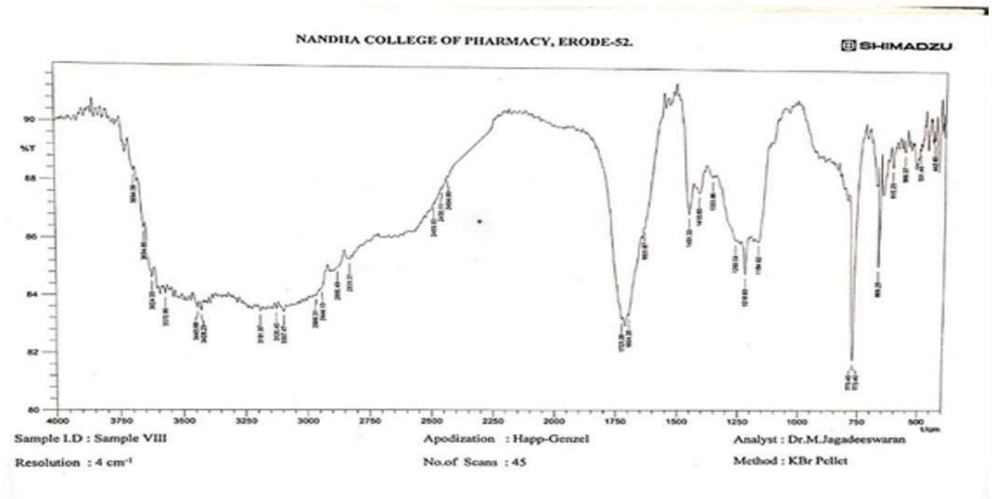

Figure.3: FTIR of Methotrexate

The pH values of all formulations ranged from 6.32 to 6.85, which falls within the normal physiological pH range of the skin. Formulation F5 showed a pH of 6.70, indicating excellent compatibility and reduced risk of skin irritation during prolonged application.

Spreadability studies demonstrated that formulations with lower viscosity exhibited higher spreadability. Formulation F5 showed balanced spreadability (13.2 g.cm/s) with adequate viscosity, ensuring ease of application and retention at the application site.

Drug content analysis confirmed uniform distribution of Methotrexate and Rutin throughout the hydrogel matrix. The drug content ranged from 93.4% to 96.3%, with F5 showing the highest drug content (96.3%), indicating efficient drug incorporation and formulation uniformity.

Viscosity measurements revealed a gradual increase in viscosity with increasing HPMC concentration. Formulation F5 exhibited an optimal viscosity of 4800 cP, providing suitable consistency for topical application while maintaining satisfactory spreadability and controlled drug release.

Functional Group	Methotrexate	Rutin	Hyaluronic Acid	HPMC	Physical measures
O-H bending	3200-3400	3200-3500	3346	3350	3370-3380
C=O stretching	1650-1700	1650-1680	1600-1650	-	1650-1700
C–O stretching	1000-1300	1000-1100	1230-1240	1150-1160	1200-1300
C–C	1060-1100	1060-1080	1068	1060	1060-1070

N–H stretching	3300-3500	-	3200-3300	-	3300-3400
C–H bending	1450-1500	1450-1500	1450	1456	1450-1470
C–H stretching	2800-3000	2900-3000	2937	2880-2900	2900-2930
Aromatic C–H bending	1500-1600	1500-1600	1456	1456	1456
Aryl ether (C–O–C)	1200-1300	1200-1270	-	1310-1326	1310-1320
C=C bending	1500-1600	1500-1620	808	807	807-808
C–N stretching	1200-1350	-	-	1456	1456
Amide C=O stretching	1650-1700	-	1606	1606	1600
O–H stretching (broad)	3200-3400	3200-3500	3420	3045-3418	3418

Table:5

In-vitro drug release studies performed using a Franz diffusion cell demonstrated sustained release of Methotrexate and Rutin over a period of 12 hours. Formulation F5 showed the highest cumulative drug release (99.1%) with a controlled and sustained release profile, whereas formulations containing higher polymer concentrations exhibited comparatively slower release due to increased matrix density.

Fig:2

Kinetic analysis of the release data using Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models indicated that drug release followed diffusion-controlled kinetics with sustained release characteristics, making the formulation suitable for prolonged therapeutic action.

Stability Studies

The optimized formulation (F5) was subjected to stability studies under refrigerated conditions for one month. The formulation retained its appearance, clarity, odor, drug content, and release characteristics throughout the study period without any significant changes. Drug content remained above 95%, and cumulative drug release remained above 97%, confirming excellent physical and chemical stability.

Time (T)	Root T	log (%) release	Log (T)	log (%) remain	Release (CumRl s / T)	1/Cum % Rls	Peppas log Q/100	% Drug Remain	Q0/1/ 3	Qt1/3	Q01/ 3-Qt1/3
0	0	0	0	0	0	0	0	0	0	0	4.64
0.5	0	1.39	-0.3	2	0	0	-0.61	100	4.64	0.64	0.00
1	0.5	1.58	0	1.88	24.67	2	-0.42	75.33	4.64	2.42	0.42

2	1	1.7	0.3	1.79	19.02	1	-0.42	61.97	4.64	3.96	0.68
4	2	1.75	0.6	1.7	12.46	0.5	-0.3	50.15	4.64	3.69	0.95
6	4	1.79	0.78	1.64	9.42	0.25	-0.25	43.47	4.64	3.52	1.13
8	6	1.88	0.9	1.58	7.77	0.17	-0.21	37.81	4.64	3.36	1.29
10	8	1.93	1	1.38	7.61	0.13	-0.12	23.94	4.64	2.88	1.76
12	10	1.98	1.08	1.15	7.15	0.1	-0.07	14.17	4.64	2.42	2.22
24	12	2	1.38	0.69	3.96	0.08	-0.02	4.92	4.64	1.7	2.94

Table:6

Overall, the results demonstrated that formulation F5 possessed optimal physicochemical properties, sustained drug release behavior, excellent stability, and superior patient acceptability, making it a promising topical drug delivery system for the management of psoriasis.

6. CONCLUSION

The present study successfully developed a Methotrexate and Rutin topical hydrogel for the treatment of psoriasis. Among all formulations, **F5** exhibited optimal characteristics with a pH of **6.70**, spreadability of **13.2 g.cm/s**, drug content of **96.3%**, and viscosity of **4800 cP**. The formulation demonstrated sustained and controlled drug release, making it suitable for long-term psoriasis management. The combination of Methotrexate and Rutin provided synergistic anti-proliferative, antioxidant, and anti-inflammatory effects. The topical hydrogel approach may reduce systemic toxicity associated with oral therapy while improving patient compliance. Thus, the optimized F5 formulation represents a promising and patient-friendly therapeutic option for localized psoriasis treatment.

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