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Preparation and In Vitro Characterization of Leflunomide Microsponges Loaded Topical Gels

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ABSTRACT
The objective of this study was to formulate and evaluate leflunomide-loaded microsponges incorporated into a topical gel to enhance skin delivery. Leflunomide, a potent anti-inflammatory agent, is commonly used in the treatment of dermatological conditions such as osteoarthritis and psoriasis. Optimized microsponges containing leflunomide were prepared and integrated into a gel base. The final topical gel formulation was assessed for pH, viscosity, spreadability, drug content uniformity, and skin permeation characteristics. The gel's pH was carefully adjusted to match skin pH, ensuring better compatibility and enhanced drug delivery. The formulated leflunomide microsponge gel exhibited promising physicochemical properties and sustained release behavior, offering the potential for prolonged therapeutic effects and improved patient outcomes. Among the six formulations developed, formulations F2 and F3 demonstrated the most favorable characteristics and were identified as optimal.

INTRODUCTION:

Novel Drug Delivery Systems (NDDS):
The primary aim of novel drug delivery systems is to efficiently deliver the required therapeutic concentration of a drug to a specific site in the body in a controlled manner over a defined period. The drug delivery system should ensure the timely and targeted release of the medication, enhancing therapeutic efficacy while minimizing side effects.

NDDS can be broadly categorized into:
a. Sustained-release drug delivery systems
b. Controlled-release drug delivery system

Sustained-Release Systems:
These systems are designed to release drugs gradually, maintaining therapeutic plasma levels over an extended period. The onset of action is delayed, and therapeutic effects are prolonged, reducing dosing frequency and improving patient compliance.

Controlled-Release Systems:
Controlled-release formulations go beyond merely sustaining drug release. They offer precise control over the rate and duration of drug delivery, providing reproducible plasma drug levels and minimizing fluctuations.

Topical Drug Delivery Systems:
Topical drug delivery is a localized approach where medications are applied directly to the skin or mucous membranes (ophthalmic, rectal, vaginal, and dermal routes). The skin, being easily accessible, serves as an ideal site for such drug delivery, especially for conditions requiring local treatment. The therapeutic effect can be local, surface-level, or systemic.

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Topical formulations typically involve a base that may have therapeutic properties on its own—such as emollient or protective effects. The base also acts as a carrier for the active pharmaceutical ingredient (API), enabling controlled and effective delivery.

Formulation types are often classified based on physical properties (e.g., suspensions), intended use (e.g., liniments), or composition (e.g., hydrophilic creams). Modern topical delivery systems aim to improve drug efficacy, patient acceptability, tolerability, and overall quality of life.

Gels as Topical Dosage Forms:
Gels are modern semisolid formulations in which large amounts of aqueous or hydro-alcoholic liquids are entangled within a three-dimensional polymeric matrix. These networks may be formed from natural or synthetic polymers or inorganic substances such as aluminum salts. Gels are often transparent and cosmetically elegant, offering improved patient compliance.

Types of Gels:
Single-phase gels: Consist of biomolecules uniformly dispersed in the liquid phase without separation.
Double-phase gels: Contain distinct colloidal particles dispersed in a continuous phase (e.g., milk of magnesia).

Microsponge Drug Delivery Systems (MDDS):
Microsponge technology represents an innovative approach in controlled drug delivery. It addresses limitations associated with traditional dosage forms such as rapid release, low bioavailability, skin irritation, and systemic side effects.

Microsponges are highly cross-linked, porous polymeric microspheres with interconnected pores that can entrap active pharmaceutical ingredients and release them at the target site in a controlled manner. These structures, generally ranging from 5 to 100 microns, are too large to penetrate the skin, ensuring that the drug is released on the skin's surface and absorbed gradually.

The release mechanism depends on diffusion through the pores, offering sustained therapeutic effects. Microsponges are typically fabricated using polymers such as Eudragit RS100, Eudragit S100, polyhydroxybutyrate, and polyvinyl benzene.

Advantages of Microsponge Technology:
Enhanced product elegance and aesthetic appeal
Reduced toxicity and irritation Improved stability and solubility of active compounds Increased bioavailability Controlled and prolonged drug release Optimized product performance with minimal active ingredient usage

MATERIAL AND METHODS:

Table 1 - List of instruments-

S.no.	Equipments	Supplier
1	Digital Balance	Shimadzu Corporation
2	IR Spectrometer	Perkin Elmer Spectrum
3	UV Vis Spectrometer	Aligent Technologies
3	Magnetic stirrer	Hixon Instrument Grover Enterprises
5	Sonicator	Sonar India
6	Dissolution apparatus	Electro lab
7	Viscometer	Brookfeild Viscometer
8	Melting point	Nutronics
9	Magnetic stirrer	Remi Equipment

Table 2- List of Chemicals

Sr.No.	Ingredients	Role in Formulation	ManufacturingSuppliers
1	Leflunomide	Active Ingredient	Solitaire Pharmacia
2	Eudragit RS100	Polymer	Central drug houselab.
3	Ethyl Cellulose	Polymer	Central drug houselab.
3	PloyvinylAlcohol	StabilizingAgent	Central drug houselab.
5	Triethyl citrate	Plasticizer	Central drug houselab.
6	Dichloromethane	Solvent	Central drug houselab.

RESULTS & DISCUSSION:

Organoleptic properties-

Table-3 – Organoleptic Properties

Sr. No.	Properties	Result
1.	Description	Solid
2.	Appearance	Fine white smooth powder
3.	Colour	white
3.	Odor	Odorless
5.	Nature	Smooth powder

Discussion: Organoleptic properties of drug was observed by physical and visual method. The observed properties were matched with the given standard observed data.

Table-4 - Solubilties studies

Sr. No	Solvents	Concentration (mg/ml)	Report
1.	Water	0.010	Insoluble
2.	DMSO	15	Soluble
3.	DMA	0.065	Soluble

Discussion : As per the observation of drug is not soluble in water, soluble in DMSO, and soluble in DMA.

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Calibration Curve of Leflunomide The calibration curve of leflunomide was prepared in DMA(N,NDimethylacetamide)

Table 5- Calibration curve of leflunomide

Sr. No	Concentration(µg/ml)	Absorbance(nm)
1	2	0.010
2	3	0.150
3	6	0.301
3	8	0.319
5	10	0.513
6	12	0.683
7	13	0.810
8	16	0.923

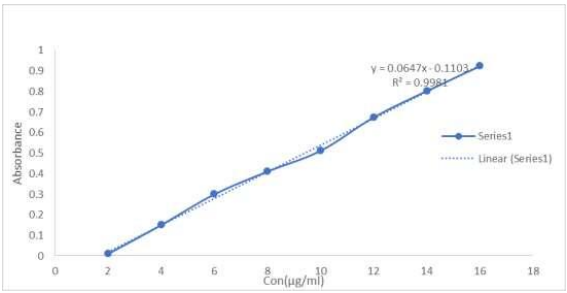

Figure 1 - Calibration Curve of the Drug

Discussion: The standard curve plot between concentration and absorbance. The value R^2 was found to be 0.9981. So, the equation can be used for the further calculation.

FTIR STUDY:

Interaction between the drug and excipients used in the formulation was studied.The result are as follows-

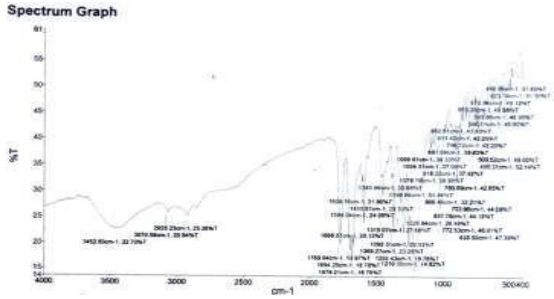

Figure 3 - FT-IR of Leflunomide and Excipients

Table-6 - PHYSICAL COMPATIBILITY

S.No.	Drug andExcipient	Description and condition			
		Initial	Room temperature(in days)		
			10	15	20
1	Leflunomide	Yellow colouredpowder	NC	NC	NC
2	EUD	White colouredgranules	NC	NC	NC
3	EC	White colouredpowder	NC	NC	NC

Figure 7 – Loading Efficiency Chart

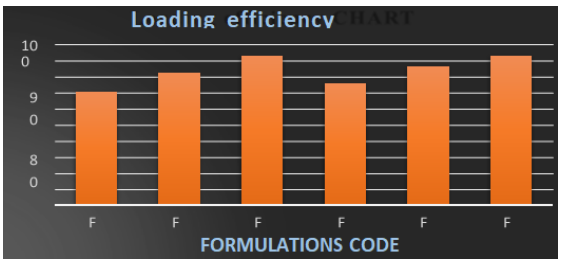

Figure 8– Microsponges

Table 8 - Percentage yield of microsponges formulation

Formulation code	Theoretical yield (g)	Practical yield (g)	Percentage yield (%)
F1	0.7	0.329	70.12
F2	0.7	0.538	77.81
F3	1.3	0.876	86.52
F3	0.6	0.392	65.31
F5	1.8	0.802	77.53
F6	1.3	1.110	85.31

Microsponges were prepared and their Percentage yield was calculated. They were found to be in the range of 70.12% to 86.52%. It shows increasing drug:polymer ratio increased the percentage yield.

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PARTICLE SIZE DISTRIBUTION-

Table 9- Size distribution F3 (Best Formulation)

Size range (µm)	Mean size (d)	No. of particles(n)	Standard deviation (nd)	Percentagefrequency
0-15	7.5	12	90	12
15-30	22.5	30	675	30
30-35	37.5	19	712	19
35-60	52.5	23	1207	23
60-75	67.5	6	305	6
75-90	82.5	10	825	10

Table - Average Particle size

Formulation	Average particle size
F1	39.13
F2	33.95
F3	33.62
F3	36.95
F5	33.03
F6	33.30

In-vitro Drug Release of Microsponge:

sTable - The in-vitro release of various formulation

Time(Hrs)	F1	F2	F3	F3	F5	F6
1	05.30	05.60	06.70	03.60	05.10	05.20
2	13.20	13.60	15.30	08.10	11.36	12.10
3	23.23	23.35	25.52	13.60	15.30	22.60
3	32.56	33.60	33.36	66.30	68.60	63.60
5	31.60	31.36	33.30	69.60	30.60	30.30
6	33.63	39.38	56.65	33.63	30.06	36.60
3	56.66	56.35	58.60	33.60	35.55	36.10
8	59.65	59.30	59.35	53.56	56.30	56.30
9	63.36	66.06	68.50	66.30	66.60	63.60
10	36.30	33.66	36.60	36.60	35.65	36.80
11	39.39	80.06	86.30	38.30	81.38	86.60
16	86.38	88.56	88.60	86.60	88.30	88.80

Evaluation of Microsponges Gel

Visual Inspection:

The prepared gel formulations of leflunomide microsponges were inspected visually for their color texture and appearance. All prepared formulations were yellow, viscous preparation with a smooth texture and showed good homogeneity with the absence of any lumps and syneresis.

Table 10- Visual Inspection

Formulationcode	Color	Consistency	Homogeneity	Appearance	Uniformity
F1	Light Yellow	Less Viscous	Good	Opaque	Good
F6	Light Yellow	OptimumViscous	Good	Opaqueyellow	Good

Spreadability and Viscosity Studies:

The value of spreadability of microsponges F1 and F6 was found to be 3.3 and and 5.0 g.cm/sec respectively, indicating the acceptable spreadability of gel.

Microsponge formulation F1 was found to be more viscous than the gel loaded with microspongeusing Eudragit RS 100

Table-11 - Spreadability and Viscosity Studies

Gel Formulation	Drug content	Viscosity (cps)	Spreadability (g.cm/sec)	pH
Gel containing Ethyl cellulose (FG1)	93.5	1380	3.3	3.8
Gel containing Eudragit RS 100 (FG6)	93.3	1393	5.0	3.3

In-vitro diffusion study for microsponge gel:

The in vitro diffusion was carried out for the formulation F1 and F6 using PBS (pH 3.3) over the period of 16 hr. It was observed that the formulation F1 showed higher amount of drug diffused atthe end of 16 hr as compared to F6 i.e., 89.30% and 96.18% respectively. Hence, the microsponge loaded gel formulation F1 was optimized formulation which shows the drug release in a controlled form with all the acceptable properties.

Table 12- In vitro study

Time (min)	Cumulative % drug release	
	F6	F3
0	0	0
30	5.33	9.33
30	9.83	63.33
630	63.33	69.33
680	33.38	33.83
330	30.36	33.63
300	33.96	33.36

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330	35.33	56.68
330	53.33	58.53
380	33.63	35.66
530	36.53	33.33
300	33.83	38.33
330	86.65	83.35
330	89.30	93.68

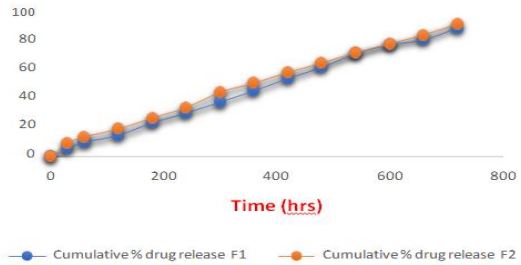

Figure 8 - cumulative % release vs time

CONCLUSION:

Leflunomide is a poorly soluble drug with short half life, thus selected as a model drug for MDDS to overcome these problems and to release the drug in a controlled manner. Leflunomide is formulated as Microsponges by Quasi emulsion solvent diffusion method using polymers Eudragit RS 600 and Ethyl cellulose and finally incorporate in gels.

- Compatibility studies were performed for drug and excipients
- Physical compatibility study showed drug and excipients were physically compatible with each other.
- Chemical compatibility study (FT-IR) was carried out. It revealed no interaction between the drug and excipients.
- Standard graph was drawn for Leflunomide and it was found that the solutions showed linearity (R^3=0.998) and obeyed Beer Lambert's law.
- Leflunomide Microsponges were prepared using two polymers to determine which polymerretards the release better.
- The *in-vitro* release was carried out for all the formulations. Therefore F3 and F3 were selected as optimized formulations.

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