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Original Article

Preparation and *in vitro* Characterization of Diacerein Microsponges Loaded Topical Gels

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ABSTRACT

Background: This study's objective was to create and assess diacerein-loaded microsponges incorporated into a topical gel formulation for enhanced skin delivery. Diacerein is a potent anti-inflammatory agent used in the management of various dermatological conditions, including osteoarthritis and psoriasis. **Materials and Methods:** The optimized diacerein-loaded Additionally, a gel basis was enhanced using microsponges and the resulting topical. The gel's pH, viscosity, spreadability and homogeneity of drug content were assessed and skin permeation studies. The topical gel's pH was changed to make sure compatibility with the skin pH for enhanced drug delivery. The prepared diacerein-loaded microsponges incorporated into a topical gel formulation showed promising characteristics for enhanced skin delivery. **Results:** Evaluation parameters like viscosity, drug content, spreadability for all the prepared formulations were assessed. Formulation F2 and F4 shows the most optimized result from all the six formulations. **Conclusion:** The sustained release pattern achieved through the microsponges technology offers the potential for prolonged therapeutic effects and improved patient outcomes in the treatment of dermatological conditions.

Keywords: Microsponges, Topical gel, Sustained release, Controlled release.

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INTRODUCTION

The novel drug delivery system

The innovative medicine delivery system's objective is to quickly carry the required drug concentration to the proper room in the body in a therapeutic amount (Figure 1). The medication should be delivered by the drug delivery system promptly. Throughout a predetermined treatment period, the body is in a regulated manner.[1]

Two distinct systems can be used for novel drug delivery:

- Sustained release medication delivery systems.
- Controlled-release drug delivery system.

Sustained Release Medication Delivery Systems

It is a medication dosage form intended to postpone the onset of a curative effect in order to maintain the plasma profile. For a extended period of time and the effect appears delayed in the systemic circulation. Its pharmaceutical activity frequently takes time to begin and its therapeutic effects last a sustained amount of time.[1]

Controlled Release Drug Delivery System

This system's significance extends beyond the realm of prolonged pharmacological action; instead, it displays probability and repeatability in the kinetically of drug release. Drug release from a controlled release drug delivery system happens at a frequency profile that is predictable from one component to the next and kinetically likely.[1]

Topical drug delivery system

Topical therapy is a targeted medication delivery approach that can be applied topically, subcutaneously, vaginally, or through the eyes. The main route for topical medicine delivery is the epidermis, which is also one of the human body's easiest organs to apply cosmetically. Topical medications are applied to the skin for effects that are surface, local, or systemic in nature. The base's medicinal qualities, such as its emollient, calming, or protecting function, may occasionally allow for its exclusive usage. The

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therapeutically effective components in many topical treatments are, however, dispersed or disintegrated into the foundation. A vast array of topical drugs that can be utilized for a variety of drug delivery and therapeutic procedures are made possible by the combination of active ingredients and substrates. Classification of topical therapies containing therapeutically active substances can be done according to composition (hydrophilic creams), physical qualities (suspension), or intended usage (liniments).In addition to being an important advance over conventional methods (creams, moisturizers, applications and pastes), These delivery methods have the power to improve efficacy and tolerability, boost patient acceptance (including the quality of life for those with dermatitis) and address other unmet needs in the market for topical dermatological.[2]

Gels

Gels are a more recent category of dosage forms that are created when large amounts of an aqueous or hydroalcoholic fluid are trapped in a network of irregular solid particles. These particles can be made of synthetic or natural organic polymers, inorganic chemicals like aluminum salts, or both. The sort of colloidal components and amount of liquid in the composition will determine the gel's physical appearance. The majority of topical gels are made with natural polymers like carbomers, which provide the product a nice, glittery, transparent appearance and are simple to remove with water from the skin. Gels are semisolid liquid-rich two-component systems. In a typical polar gel, an organic or synthetic polymeric forms a three-dimensional matrix over anhydrous liquid.[3]

Types

Single phase gels- Gels in which there are no visible barriers separating the particles from the liquid and biomolecules are uniformly distributed throughout the liquid.

Double phase gels- Gel material is made up of bubbles of little unique pieces known as the magma. (Magnesia milk).

Microsponges Drug Delivery Systems

Every day, a vast array of new pharmacological classes are being developed as pharmaceutical delivery technologies develop. For a drug to be successful under any circumstances, a novel medication release mechanism with computed predetermined ratios at various points of function must be developed.[4] Most conventional dosage forms are unrefined and contain a number of disadvantages, including reduced bioavailability, stomach and skin irritation, unpleasant reactions and negative effects of the active components. These include tablets, capsules, creams, lotions and gels with quick release.[5] Microsponges, which are similarly composed of collapsible structures loaded with an active medicinal component, are highly cross-linked, polymeric permeable microspheres with several interconnected gaps. Microsponges' porous surface enables a range of active pharmaceutical compounds to be kept in and released in a variety of quantities at the unique absorption location. The continuous pattern of open pores in the microsponges, which varies in size, permits the medicine to be held inside and release at a controlled rate.[6]

This microsponges formulation has an active component that releases in a controlled manner. Medication delivery via microsponges involves the use of small, inactive spherical compositions that do not irritate the skin film. These combinations were developed to use the least amount of medication possible while delivering the active ingredients at the administration site.[7] A scientist named Richard Won invented microsponges. The diameter of the bead ranges from 5 to 100 m. A human sin is about five microns in size on average. The skin is impervious to the everlasting spheres. The active chemicals encircled by the pores are progressively absorbed by the skin. The polymers used in the microsponges' production are what allow them to form cages. The most often used polymers for manufacture are E-RS100, E-RS PO, E-S100, polyhydroxy butyrate and polyvinyl benzene.[8]

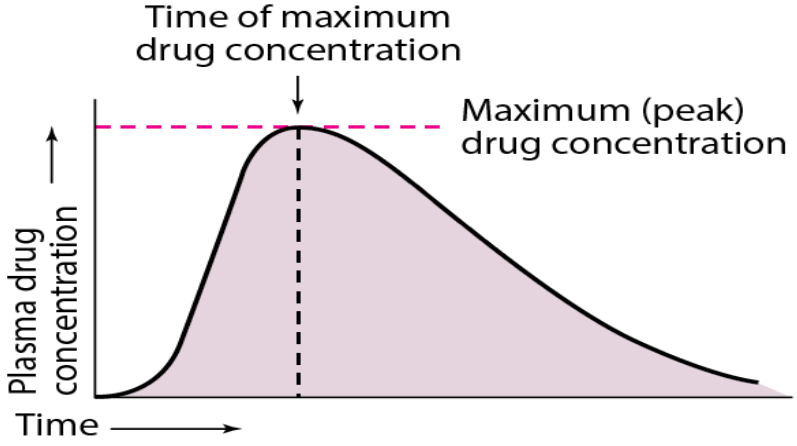

Figure 1: Plasma Concentration. vs Time.

- Advantage of microsponge technology.[9-11]
- The elegance of the product is enhanced.
- The microsponges have less toxicity.
- Increased stability and solubility of drugs.
- Microsponges enhance the active medicinal components' bioavailability.
- The microsponges enhance product performance.

MATERIALS AND METHODS (TABLES 1, 2)

Methodology

- Preformulation studies related to drug (Table 3),
- Solubility studies (Table 4),
- Standard curve (Table 5, Figure 2),
- Identification of pure drug, FTIR Analysis (Tables 6, 7),
- Preparation of microsponges gel,
- Evaluation of microsponges gel,
- Physical properties,
- pH,
- Spreadability,
- Viscosity,

Table 1: List of instruments.

Sl. No.	Equipment's	Supplier
1	Digital Balance.	Shimadzu Corporation.
2	IR Spectrometer.	Perkin Elmer Spectrum.
3	UV Vis Spectrometer.	Aligent Technologies.
4	Magnetic stirrer.	Hixon Instrument Grover Enterprises.
5	Sonicator.	Sonar India.
6	Dissolution apparatus.	Electro lab.
7	Viscometer.	Brookfield Viscometer.
8	Melting point.	Neutronics.
9	Magnetic stirrer.	Remi Equipment.

- Drug content,
- Particle size,
- Loading efficiency,
- Production yield,
- *In vitro* drug release study,
- Evaluation of microsponges.

Production yield (Table 8)

By calculating the initial weight of raw materials and the final weight of microsponges, one can calculate the percentage yield. The formula can be used to get the percentage yield.

$$\textbf{Production yield} = \frac{Practical\ yield \times 100}{\text{Theortical Yield}}$$

Loading Efficiency (Figure 3, Table 9)

Using spectrophotometry, the microsponges were identified (λ_{max}=255 nm). After dissolving 100 mg of DCN microsponges in 100 mL of phosphate buffer (pH 6.8), the sample was stored for the entire night. The real drug content in the microsponge was calculated and expressed. The following formula was used to determine the microsponges' loading efficiency (%).

$$\text{Loading efficiency} = \frac{\text{Actual drug content in microsponges} \times 100}{\text{Theortical drug content}}$$

Particle size analysis (Tables 10-16)

Using an optical microscope and a calibrated ocular and stage micrometer, the average particle size of Diacerein-loaded microsponges was ascertained. A cover slip was placed on a spotless glass slide that had a small amount of microsponges spread out on it along with a drop of liquid paraffin. In order to determine the average particle size, measurements 100 particles of each batch. $d_{av}=\Sigma\ nd/\Sigma n$ Where, d_{av} is the average diameter of particles (μm), n is a number of particles per group and d is the middle value (μm). IV.

Evaluation of Gel

PH measurement

A digital pH meter was utilized to ascertain the pH of the gel composition. After dissolving 1 g of gel in 100 mL of distilled

Table 2: List of Chemicals.

Sl. No.	Ingredients	Role in Formulation	Manufacturing Suppliers
1	Diacerein	Active Ingredient.	Solitaire Pharmacia.
2	Eudragit RS 100.	Polymer	Central drug house lab.
3	Ethyl Cellulose.	Polymer	Central drug house lab.
4	Polyvinyl Alcohol.	Stabilizing Agent	Central drug house lab.
5	Triethyl citrate.	Plasticizer	Central drug house lab.
6	Dichloromethan e.	Solvent	Central drug house lab.

water, it was kept for two hours. It was measured how acidic the formulation was.

Appearance

Color matters when it comes to patient compliance. The produced gels were examined visually to ensure they were clear, colored and free of any particles.

Drug content

1 g of microsponge gel was precisely weighed, dissolved in methanol and then sonicated for 10-15 min. The resulting mixture was then added to a one hundred millilitre volumetric flask using methanol. To reach a concentration within Beer's range, 10 mL of this was pipetted out and diluted to 100 mL using methanol. The final dilution was made with distilled water. Using a blank gel that had been prepared in the same way as the sample, the absorbance was measured at 255 nm using a UV spectrophotometer.

Viscosity measurement (Table 17)

The viscosity of the various gel compositions was measured at 25°C using a Brookfield viscometer with spindle no. 64 running at 100 rpm. Using a Brookfield viscometer, the optimal formulation's viscosity was ascertained without dilution. (Model-LVDV-E). The Brookfield Viscometer is made comprised of a spinning spindle and a fixed cup. Rotating spindles of varying sizes are employed and submerged in the test substance. big size spindles (big diameter and surface area) are used for low-viscosity liquids, whereas small spindles (small diameter and surface area) are used for high-viscosity liquids. Turn the spindle inside the microsponge gel until the viscometer's dial readout remains constant. For repeatable results, repeat this process three times.

Spreadability studies (Table 17)

Good spreadability is one of the requirements for a gel to satisfy the ideal attributes. This phrase is used to describe the area that gel spreads easily when applied to the skin or other affected area. The spreading value of a formulation also affects how effective it is as a medicine. Spreadability is measured in terms of the number of seconds it takes for two slides to separate from gel that has been positioned between them when a specific stress is applied. Better spreadability results from separating two slides in less time. The formula below was then utilized to determine spreadability:

$$S=M \times L/T$$

Where, S=Spreadibility, M=Weight in the pan, L=Length moved by the glass slide, T=Time taken to separate slide completely.

RESULTS AND DISCUSSION

Organoleptic properties of Diacerein

Table 3: Organoleptic Properties.

Sl. No.	Properties	Result
1.	Description	Solid
2.	Appearance	Fine yellow smooth powder
3.	Colour	Yellow
4.	Odor	Odorless
5.	Nature	Smooth powder

Discussion: The drug's organoleptic qualities were examined using both visual and physical methods. The provided standard observed data and the observed attributes matched.

Table 4: Solubilities studies.

Sl. No.	Solvents	Concentration (m g/mL)	Report
1.	Water	0.010	Insoluble
2.	DMSO	15	Soluble
3.	DMA	0.065	Soluble

Discussion: The medication is not soluble in water, soluble in DMSO and soluble in DMA, according to observations.

Calibration Curve of Diacerein (Table 5)

The calibration curve of diacerein was prepared in DMA (N, N-dimethylacetamide).

Table 5: Calibration curve of diacerein.

Sl. No.	Concentration (µg/mL)	Absorbance (nm)
1	2	0.0096
2	4	0.1499
3	6	0.2992
4	8	0.4101
5	10	0.5111
6	12	0.6738
7	14	0.8021
8	16	0.9224

Discussion: The concentration and absorbance standard curve graphic. R2 was discovered to be 0.9981. Thus, the formula can be applied to more calculations.

FTIR STUDY

It was investigated how the drug and the formulation's excipients interacted. The following are the outcomes (Figures 4, 5, 6):

Prepared Microsponges: Microsponges were prepared using Quasi emulsion solvent diffusion method (Figure 7).

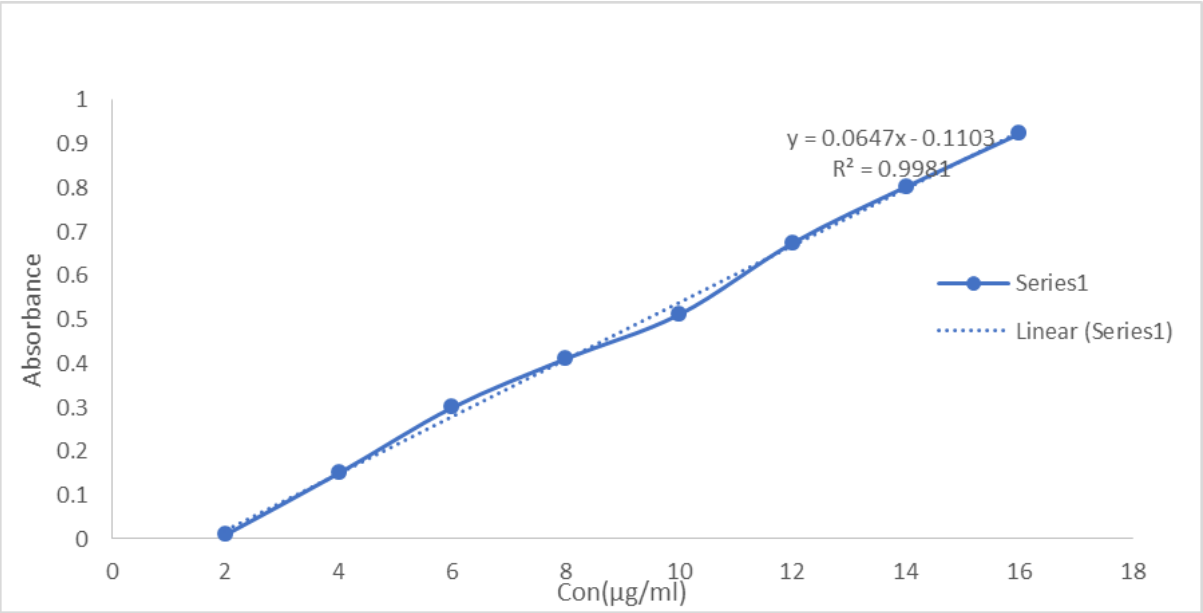

Figure 2: Calibration Curve of Diacerein.

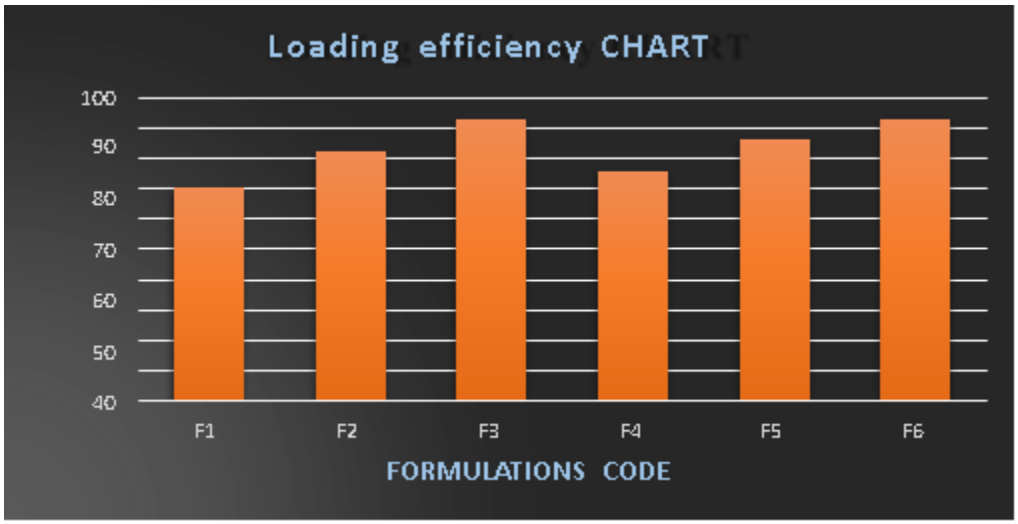

Figure 3: Loading Efficiency Chart.

Internal Phase: Diacerein (100 mg) and Ethyl cellulose (200 mg F1, 250 mg F2, 300 mg F3) / Eudragit RS 100 (200 mg F4, 250 mg F5, 300 mg F6) in Dichloromethane (20 mL).

External Phase: Polyvinyl alcohol in distilled water, (0.75% w/v).

Percentage Yield

After preparing the microsponges, the yield percentage was determined. They were discovered to be between 70.12% and 86.52%. It displays rising drug usage: The percentage yield rose with the polymer ratio.

Loading Efficiency

The range of loading efficiency was 70.41 to 92.66%. The formulations F3 and F6 were determined to have the highest loading efficiency. This demonstrates that loading efficiency rose as the drug: polymer ratio grew.

Evaluation of Microsponges Gel

Visual Inspection (Table 19)

The color, texture and appearance of the obtained gel formulations of diacerein microsponges were examined visually. Each created formulation had a smooth texture, was yellow and exhibited good homogeneity-no lumps or syneresis-as well as viscosity.

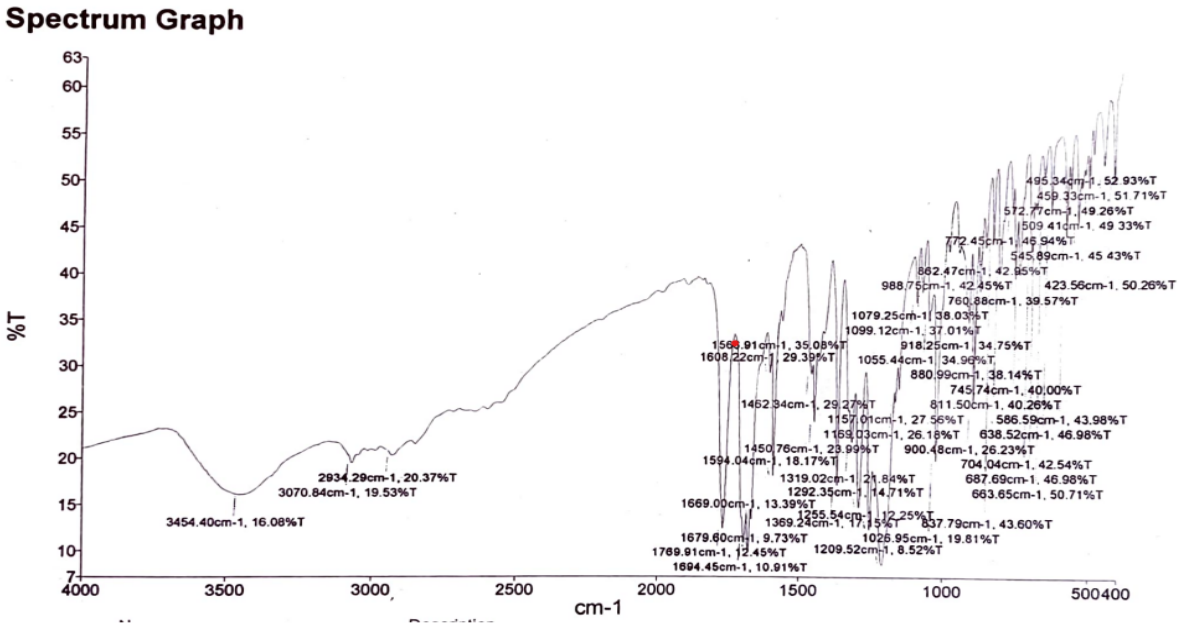

Figure 4: FT-IR of diacerein.

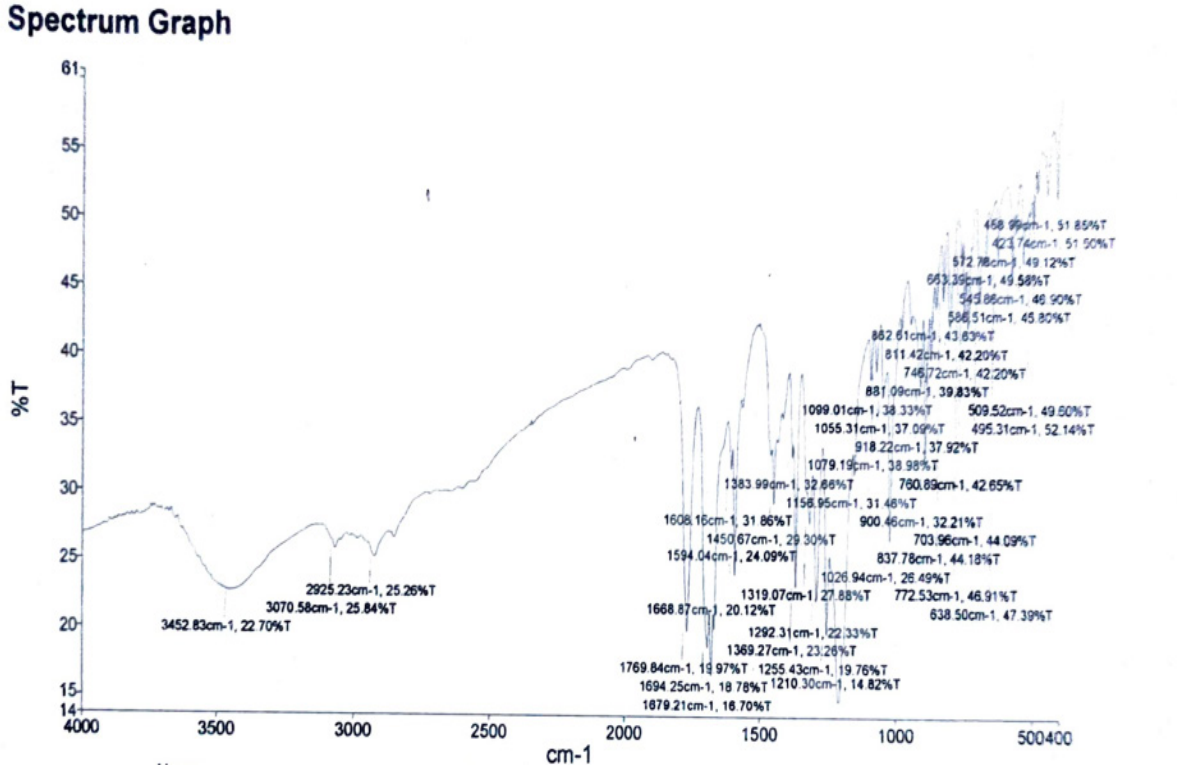

Figure 5: FT-IR of Diacerein and Ethyl Cellulose.

Table 6: Interpretation data.

Sl. No.	Drug	Drug+EC	Drug+EUD	Types of Vibration
1	1769.91	1769.84	1769.05	C=O Stretching
2	3428.04	3452.83	3454.04	O-H Stretching
3	1210.38	1210.03	1209.52	C- O Stretching

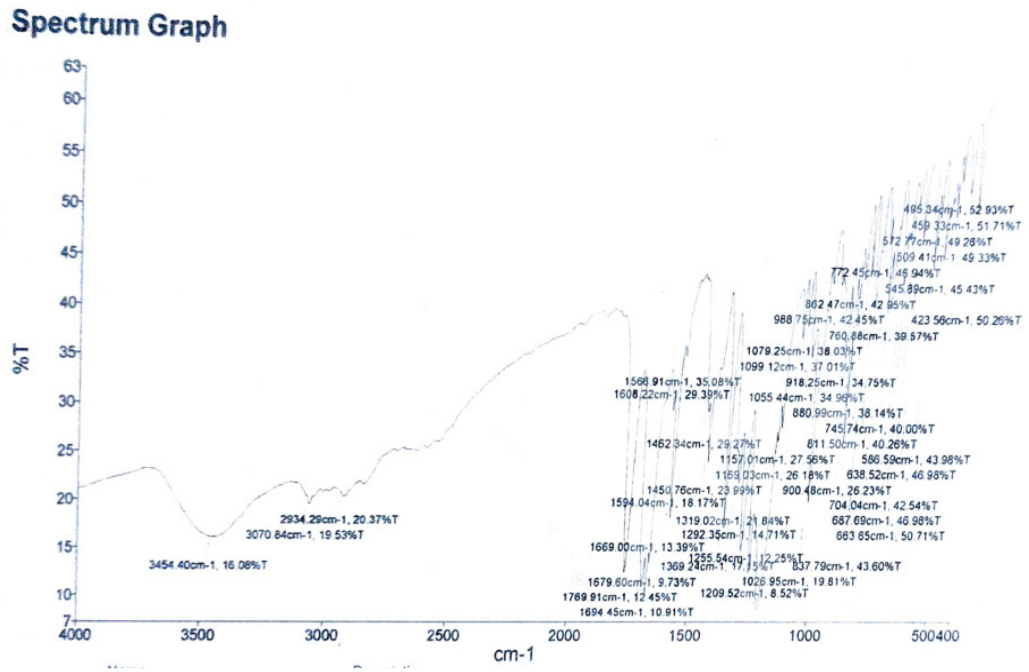

Figure 6: FT-IR of Diacerein and Eudragit RS100.

Table 7: Physical Compatibility.

Sl. No.	Drug and Excipient	Description and condition			
		Initial	Room temperature (in days)		
			10	15	20
1	DCN	Yellow coloured powder	NC	NC	NC
2	EUD	White coloured granules	NC	NC	NC
3	EC	White coloured powder	NC	NC	NC
4	PVA	White coloured powder	NC	NC	NC
5	DCN+EUD	Yellow coloured powder	NC	NC	NC
6	DCN+EC	Yellow coloured powder	NC	NC	NC
7	DCN+PVA	Yellow coloured powder	NC	NC	NC

Table 8: Percentage yield of microsponges formulation.

Formulation code	Theoretical yield (g)	Practical yield (g)	Percentage yield (%)
F1	0.6	0.421	70.12
F2	0.7	0.545	77.81
F3	1	0.865	86.52
F4	0.6	0.392	65.31
F5	1	0.775	77.53
F6	1.3	1.110	85.31

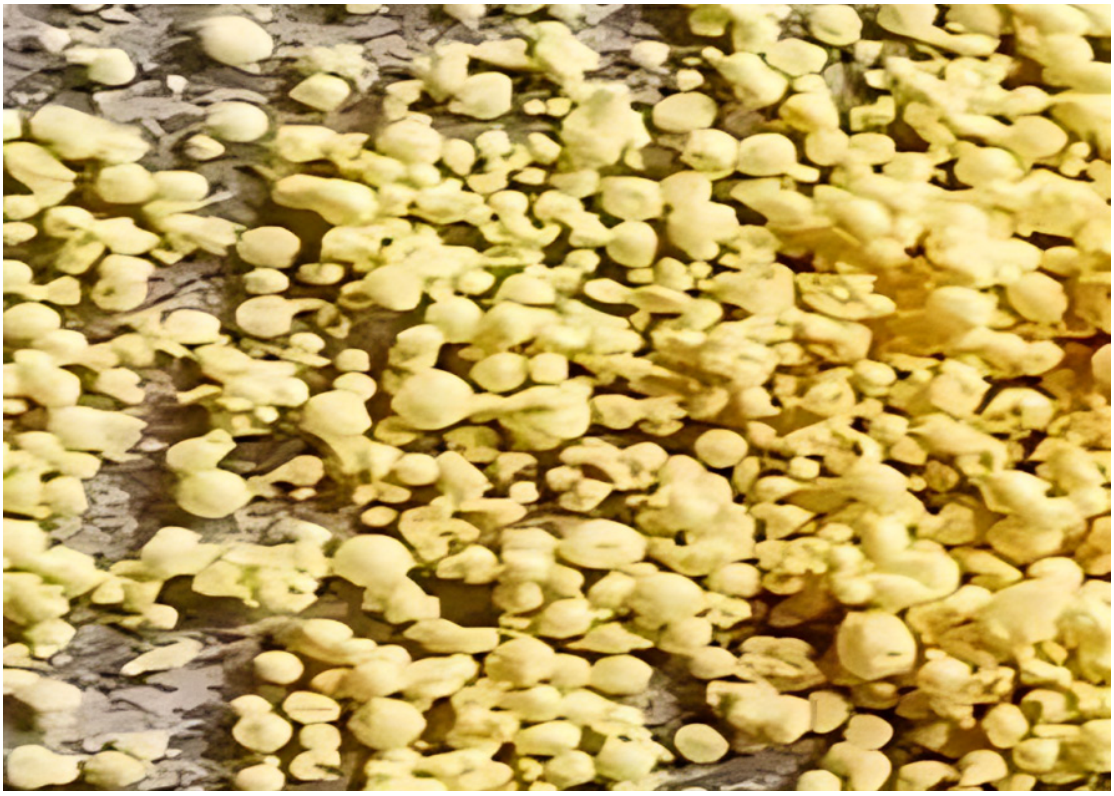

Figure 7: Microsponges.

Spreadability and Viscosity Studies

The value of spreadability of microsponges F1 and F2 was found to be 7.4 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 microsponge using Eudragit RS 100.

Table 9: Loading efficiency.

Formulation code	Loading efficiency (%)
F1	70.41
F2	82.32
F3	92.56
F4	75.80
F5	86.38
F6	92.66

In vitro diffusion study for microsponge gel (Figure 8, Table 20)

Using PBS (pH 7.4), the *in vitro* diffusion was done for the formulations F1 and F2 over a 12-hour period. At the end of the 12-hour period, formulation F1 was found to have more drugs diffused than the formulation F2, with percentages of 89.40% and 92.18%, respectively. As a result, the microsponge loaded gel formulation F1 was refined to provide regulated drug release with all desired characteristics.

Particle size distribution

Table 10: Size distribution F1.

Size range (µm)	Mean size (d)	No. of particles (n)	Standard deviation (nd)	Percentage frequency
0-15	7.5	12	90	12
15-30	22.5	30	675	30
30-45	37.5	19	712	19
45-60	52.5	23	1207	23
60-75	67.5	6	405	6
75-90	82.5	10	825	10

Σn= 100 Σnd=3914. Σnd/Σn=3914\100=39.14 µm.

Table 11: Size distribution F2.

Size range (µm)	Mean size (d)	No. of particles(n)	Standard deviation (nd)	Percentage frequency
0-15	7.5	12	90	12
15-30	22.5	36	810	36
30-45	37.5	21	787.5	21
45-60	52.5	23	1207.5	23
60-75	67.5	4	270	4
75-90	82.5	4	330	4

Σn= 100 Σnd=3495. Σnd/Σn=3495\100=34.95 µm.

Table 12: Size distribution F3.

Size range (µm)	Mean size (d)	No. of particles (n)	Standard deviation (nd)	Percentage frequency
0-15	7.5	11	82.5	11
15-30	22.5	42	945	42
30-45	37.5	24	900	24
45-60	52.5	12	630	12
60-75	67.5	7	472.5	7
75-90	82.5	4	330	4

Σn= 100 Σnd=3360. Σnd/Σn=3360\100=33.6 µm.

Table 13: Size distribution F4.

Size range (µm)	Mean size (d)	No. of particles (n)	Standard deviation (nd)	Percentage frequency
0-15	7.5	6	45	6
15-30	22.5	10	225	10
30-45	37.5	29	1087.5	29
45-60	52.5	30	1575	30
60-75	67.5	20	1350	20
75-90	82.5	5	412.5	5

Σn= 100 Σnd=4695.Σnd/Σn=4695\100=46.95 µm.

Table 14: Size distribution F5.

Size range (µm)	Mean size (d)	No. of particles (n)	Standard deviation (nd)	Percentage frequency
0-15	7.5	6	45	6
15-30	22.5	27	607.5	27
30-45	37.5	20	750	20
45-60	52.5	25	1312	25
60-75	67.5	15	1012.5	15
75-90	82.5	7	577.5	7

Σn= 100 Σnd=4304.Σnd/Σn=4304\100=43.04 µm.

Table 15: Size distribution F6.

Size range (µm)	Mean size (d)	No. of particles (n)	Standard deviation (nd)	Percentage frequency
0-15	7.5	14	105	14
15-30	22.5	35	787.5	35
30-45	37.5	26	975	26
45-60	52.5	18	945	18
60-75	67.5	4	270	4
75-90	82.5	3	247.5	3

Σn= 100 Σnd=3330.Σnd/Σn=3330\100=33.30 µm.

Average particle size of microsponges formulations

Table 16: Average Particle size.

Formulation	Average particle size
F1	39.14
F2	34.95
F3	33.62
F4	46.95
F5	43.04
F6	33.30

Table 17: Spreadability and Viscosity Studies.

Gel Formulation	Drug content	Viscosity (cps)	Spreadability (g.cm/sec)	pH
Gel containing Ethyl cellulose (FG1)	92.5	1380	7.4	6.8
Gel containing Eudragit RS 100 (FG2)	93.2	1296	5.0	6.7

In vitro drug release of microsponges: (Table 18)

Table 18: The *in vitro* release of various formulations.

Time (Hr)	F1	F2	F3	F4	F5	F6
1	05.30	05.60	06.70	03.60	05.10	05.20
2	13.20	14.60	15.30	08.10	11.36	12.10
3	23.24	24.45	25.52	13.60	15.40	22.60
4	32.56	33.60	33.72	26.40	28.60	27.20
5	41.20	41.36	43.30	29.60	30.20	30.40
6	47.24	49.38	52.65	37.24	40.06	42.60
7	56.66	56.75	58.60	44.20	45.55	46.10
8	59.25	59.40	59.75	54.52	56.40	56.30
9	64.36	66.06	68.50	62.70	66.60	67.20
10	72.40	74.66	76.20	72.20	75.25	76.80
11	79.39	80.02	82.30	78.40	81.48	82.20
12	82.78	88.56	88.60	82.60	88.40	88.80

Table 19: Visual Inspection.

Formulation code	Color	Consistency	Homogeneity	Appearance	Uniformity
F1	Light Yellow	Less Viscous	Good	Opaque	Good
F2	Light Yellow	Optimum Viscous	Good	Opaque yellow	Good

Table 20: *In vitro* study.

Time (min)	Cumulative % drug release	
	F1	F2
0	0	0
30	5.62	9.42
60	9.86	13.67
120	14.77	19.22
180	23.38	26.82
240	30.21	34.14
300	37.91	44.71
360	45.74	51.18
420	54.22	58.53
480	62.12	65.11
540	71.56	72.34
600	77.82	78.43
660	81.15	84.65
720	89.40	92.18

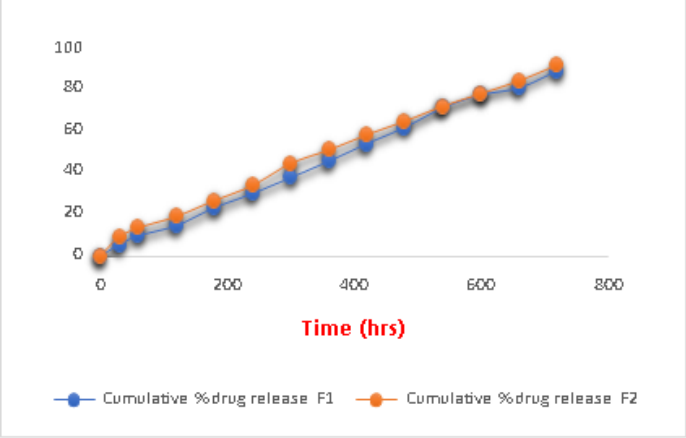

Figure 8: Cumulative % release vs time.

CONCLUSION

Diacerein was chosen as a model drug for MDDS to address these issues and enable controlled drug release because it has a short half-life and is poorly soluble in water. Using the polymers Eudragit RS 100 and Ethyl cellulose, diacerein is prepared as microsponges by the quasi-emulsion solvent diffusion process, which is then incorporated into gels. Compatibility studies were performed for drug and excipients.

A physical compatibility investigation revealed that there was no physical conflict between the medicine and the excipients.

An analysis of chemical compatibility (FT-IR) was conducted. There was no evidence of a drug-excipient interaction.

A standard graph was created for Diacerein and it was discovered that the solutions adhered to Beer Lambert's law and demonstrated linearity (R^2=0.998).

Diacerein Microsponges were made using two different polymers to see which one best delay the release.

For every formulation, the *in vitro* release procedure was completed. Therefore, F2 and F4 were selected as optimized formulations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

µm: Micrometre; **m g/mL:** Milligram/milliliter; **%:** Percentage; **EC:** Ethyl Cellulose; **EUD:** Eudragit; **DCN:** Diacerein; **Con/Conc.:** Concentration, **NC:** No Change.

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