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In-vitro release study of Diacerein loaded Microemulsion based hydrogels in the treatment of Osteoarthritic

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ABSTRACT

Background: The prime goal of this work is to improve the effectiveness of Diacerine by delivering it to the targeted topical site by applying a microemulsion-based hydrogel system and at the same time reduce the risk of adverse drug-related effects.

Materials and Methods: Micro emulsion-based hydrogels (MBH) formulations had generated significance as a possible topical delivery system. For the preparation of hydrogels, Carbapol 934P was used as a gelling agent to fabricate the MBH for enhancing the Microemulsion's (ME) viscosity for topical delivery system for the osteoarthritis treatment. To optimized the MBHs, standard parameters such as viscosity, spreadibility, in-*vitro* drug release research, and stability research.

Results: The drug release method from MBHs was pragmatic in that it follows zero-order kinetics. The prepared MBHs demonstrated better-quality stability over the 3 month period. The result shown average globule size as well as zeta potential of prepared ME (Microemulsion) has been found to be 20.98 nm and -5.55 mv, and drug release from ME within 6 hr was observed at 87% as a literature survey.

Conclusion: The result data indicates that MBH has a prospective for continued release of the drug as well as it can proceed as a hopeful vehicle for the topical delivery system of Diacerine in the osteoarthritis treatment.
Keywords: Microemulsions, Osteoarthritis, Drug release, Microemulsion-based Hydrogel, Diacerine, Topical delivery system

1. INTRODUCTION

About 10% of adults in the 55–60 age range have osteoarthritis, a degenerative joint condition that is one of the most common forms of arthritis. Hip and knee osteoarthritis is ranked as the 12th most common cause of disability. It is identified by articular cartilage damage, subchondral bone changes and synovitis. NSAIDs (Non-steroidal anti-inflammatory drugs) and other concurrent therapies provide clinical relief without stopping joint damage from developing. Furthermore, it is well known that NSAIDs might irritate the gastrointestinal tract by inhibiting the cyclooxygenase enzyme. Delivering the medication's therapeutic activity to the appropriate location in the body is the primary objective of any delivery system to quickly reach and then sustain the required drug concentration in the body [1-4]

Diacerine, sometimes referred to as diacetylrhein, is a novel analgesic, anti-inflammatory, as well as antipyretic medication utilized to treat osteoarthritis. It is 4,5-diacetoxy-9,10-dihydro9,10-di-oxo-2-anthracenecarboxylic acid. Diacerine was marginally but considerably more efficacious than a placebo, according to a 2005 Cochrane review. There is some evidence that diacetamine can reduce discomfort and halt the course of osteoarthritis (hip). It differs from NSAIDs and other traditional pharmacological therapies due to its unique way of action [3-7]

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Not among the NSAIDs (non-steroidal analgesic inflammatory drugs) that could disrupt the degenerative progression of osteoarthritis, it was thought to be a slow-acting anti-arthritic [4] Diarrhea is the most frequent adverse effect of the medication used to treat the GIT.

The systematic or IUPAC name of diacerine was 4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid. The formula is $C_{19}H_{12}O_8$. The molecular weight of diacerine was 368.294 g/mol, and it could be administered orally and excreted by the kidneys at 30%. By the Biopharmaceutical Classification System, diacerine is a class II drugs that has a high permeability and a low water solubility. As a result, diacerein's limited solubility and bioavailability raise the risk of increased rhein formation and accumulation in the large intestine, exacerbating its negative effects. Their half-life was 4–10 hours, and their total clearance was 1.5L/h and their renal CL was 0.1 L/h [3,5-7].

For improvement in keeping them on the skin, MEs could be further incorporated into hydrogels.

Because of their smaller droplet size, which ensures direct contact with the SC (Stratum Corneum) and promotes drug delivery to the skin, ME-based devices are extensively developed and studied for topical drug administration. MEs may be further integrated into hydrogels for enhancement of their skin retention [8-14]. Formulations of MBH are gaining much attention as a possible topical delivery method. The most commonly mentioned advantages of MEs are their high diffusion as well as absorption, optical clearing, thermodynamic stability, and ease of production when compared to other cutting-edge drug delivery systems. Additionally, it has been reported that ME components can reduce the stratum corneum diffusion barrier and increase drug permeation[15-19] This study was performed to improve the effectiveness of Diacerine by delivering it to the site of target applying an ME-based hydrogel system and at the same time reduces the risk of adverse drug-related effect.

1. MATERIALS AND METHOD

2.1 Materials: The gift sample of diacetone was acquired from Cipla Pharmaceuticals in Mumbai, India. Ideal Chemical in Raipur, India, provided the analytical reagents potassium dihydrogen phosphate, sodium hydrogen phosphate, and ethanol. Every analytical-grade reagent and solvent employed complied with pharmacopoeial standards.

2.2 Solubility studies

An excess of 1 mg diacerine was added to a 2mL microtube that contained 1mL of every vehicle to conduct solubility tests. To aid in solubilization, the mixture was vortexed and then stored in the shaking water bath for 3days at 37°C. Undissolved diacerine was eliminated from the samples by centrifuging them for 10 minutes at 10,000 rpm. To quantify the amount of diacerine using UV spectroscopy at 251 nm, the supernatant has been gathered, diluted utilizing methanol up to ten times, and then kept for filtration utilizing Whatman filter paper [19-22].

2.3 Method of preparation of microemulsion (ME)

The drug has been dissolved in the lipophilic part of the ME, that means the oil and aqueous phases can be combined with the surfactant and then the co-surfactant is slowly added with gradual mixing until the system is transparent. 1 g of diacerine was taken and mixed with 16 g of surfactant and 06 g of surfactant. A sufficient amount of 12 g of distilled water is mixed, all components are mixed in its so-called water phase. In another beaker, 12 g of castor oil was weighed as the oil phase. Mixing with a mechanical stirrer at 300 rpm in the aqueous phase is continued. And with constant stirring, the oil phase is mixed drop by drop to the aqueous phase. The solution was then kept under constant stirring for 4 hours. One drop of the solution was left and observed under an optical microscope. Finding and seeing spheres at the onset of ME [23-25].

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2.3 Development of Microemulsion based Hydrogel[23-25]

In Table 1, MBH formulations are gaining a lot of interest as a possible topical administration method. For a minimum of four hours, carbapol 934p was hydrated in a set volume of water. The pre-formulated ME was then gradually added with constant stirring. A clear, viscous solution is achieved by stirring it. Lastly, to create hydrogel-thickened ME, a predetermined quantity of triethanolamine was added.

Table no 1: Formulations for Microemulsion based Hydrogel (MBH)

S.no	Drugs/Chemicals	Quantity in gm
1.	Carbapol 934p	1.5 gm
2.	Water	48 gm
3.	Microemulsion	50 gm
4.	Triethanolamine	0.5 gm

2.4 Evaluation of Micro emulsion based Hydrogel[23-25]

2.4.1 Physical assessment

Visual inspection was done on physical characteristics like color, appearance, and consistency.

2.4.2 Viscosity

Viscosity was measured using a Brookfield viscometer. At room temperature, spindle #2 rotated at 5, 10, 25, and 30 rpm while submerged in ME. A number 6 spindle has been submerged in preparation along with revolved at room temperature at 5, 10, 25, and 30 rpm to test the hydrogel viscosity. The MBH's viscosity has been calculated utilizing a Brookfield viscometer. A spindle number LV4 was used to measure the viscosity of MBH after 175 g of the substance was added to a 250 ml beaker [26-28]

2.4.3 pH

A calibrated digital pH meter had been utilized to test the pH of aqueous solution (1%) of the formulation at a steady temperature.[26-28]

2.4.4 Wash ability

After applying the mixture to the skin, the ease and extent of water washing were physically assessed. [26-33]

2.4.5 Homogeneity

After the produced gel was placed into a vial and spread out on a glass slide for appearance, it was visually inspected for homogeneity and checked for lumps, flakes, or aggregates. [26-33]

2.4.6 Stickiness

At room temperature after applying two milliliters of the product to a glass plate, it was left to stand for eighteen hours at a consistent temperature and specified ambient humidity. By applying the thumb to the film and taking it off again, stickiness was further assessed subjectively utilizing the following scale:
0=No stickiness
1=Low stickiness
2=Medium stickiness

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3=High stickiness[16]

2.4.7Spreadability

Gel (1ml) was weighed and placed on a glass plate and using another glass plate with an angle of 45 degrees, the gel was spread and observation was made. Spreadability was measured as the number of seconds needed to separate the 2 sides. The following formula was utilized to get the spreadability parameter:

S = (m×l)/t

where *S* represents spreadability; to upper slides, ***m*** denotes weight tied; ***l*** denotes the length of a glass slide along with; ***t*** denotes time taken in s.[26-33]

2.4.8 Drug Content

In a volumetric flask (10mL) with methanol (5mL), MBH equal to diacerine (10 mg) was mixed, as well as the mixture was swirled for 30mins. Next, add 10 milliliters of methanol to make the volume equal to 10ml. 10ml of methanol was added to 0.1ml of the aforesaid solution to dilute it to 10µg/ml. After passing the resultant solution through Whatman filter paper, a UV spectrophotometer was applied for the detection of the solution's absorbance at 251nm. [34-36]

2.4.9 In vitro drug release studies

A Franz diffusion cell with cellophane sheets was utilized for *in vitro* drug release experiments. Two arms, one for a sample and one for the thermometer made up the 25 mL total capacity of the water-jacketed receiving chamber. The internal diameter of the donor chamber was 2 cm. The donor compartment was placed so that it barely made contact with the receptor compartment's diffusion medium. The pH 6.5 PBS (phosphate-buffered saline) in the receptor compartment was kept at 37°C ± 1°C. Before applying MBH equal to 10 mg of medication on the donor side, the membrane was equilibrated. Using a spectrophotometer set at 251 nm, samples were regularly taken out of the receptor compartment, replaced by an equivalent volume of brand-new PBS solution, as well as examined [34, 36-41].

2.4.10 Stability studies

The formulations performed similarly well in terms of pH, viscosity, homogeneity, extrudability, and appearance. Thus it was selected for stability studies. At room temperature, stability tests were conducted on the resulting gel formulation. For two months, the stability investigation was conducted. Parameters such as appearance, viscosity, pH, and spreadability were tested every month[41-42]

2.4.11 Statistical analysis

ANOVA (One-way analysis of variance) had been employed to examine the data acquired for different formulations [42]

3. RESULTS AND DISCUSSION

3.1 Solubility studies: The findings of the solubility studies analyzed their curve, which was performed and shown on (Table No. 2 and Fig No. 1) ethanol, aqueous, and hydroethanolic solution with a ʎ max 251 nm UV spectrophotometer.

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Table no 2 : Solubility Studies of Diacerine

Solvent	Water	Ethanol	Hydroethanolic Solution
Amount of Drug Present	1.267	0.566	0.090

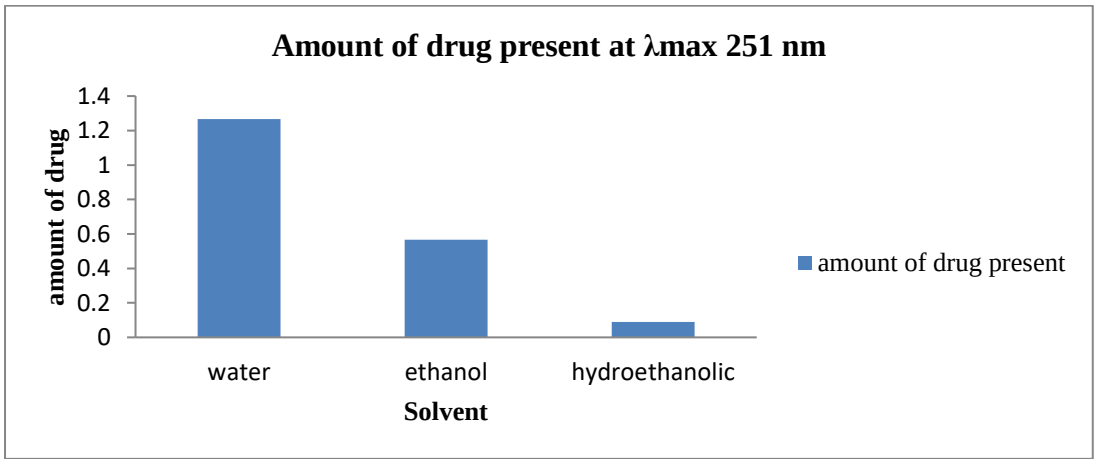

Fig.1-Solubility Studies of Diacerine in different solvents (Water, Ethanol and Hydroethanolic) at 25l nm

3.2 Evaluation of Microemulsion based Hydrogel of Diacerine globule size, zeta potential and % transmittance

Utilizing a UV spectrophotometer, the produced MBH displayed 93.6% transparency at 622 nm, a globule size of 20.98nm, and a zeta potential of -5.55mv using a Malvern particle size analyzer. The system was stable if the zeta potential was negative, which means that the ME globules were charge-free. The ME was determined to be stable since the globules did not flocculate because they were charge-free. The findings are displayed in Table No. 3.

Viscosity and pH

The prepared MBH's viscosity utilizing a Brookfield viscometer was found to be 7615 ± 12.35 cps and is shown in Table 3. It was observed that the MBH with Carbopol 934p had good quality of viscosity. Therefore, it was chosen as appropriate for the topical application. Table 3 displays the pH of the produced formulation, which had been determined to be 5.9, that is closer to the skin pH.

***In-vitro* drug release studies**

Diacerine, ME, and MBH underwent a 6-hour *in vitro* drug release investigation at 37±1˚c. At 0, 15, 30, 45, 60, and 75 minutes, samples were collected. Table no. 4 and Figure no. 2 display the formulation's comparative diacerine release profile.

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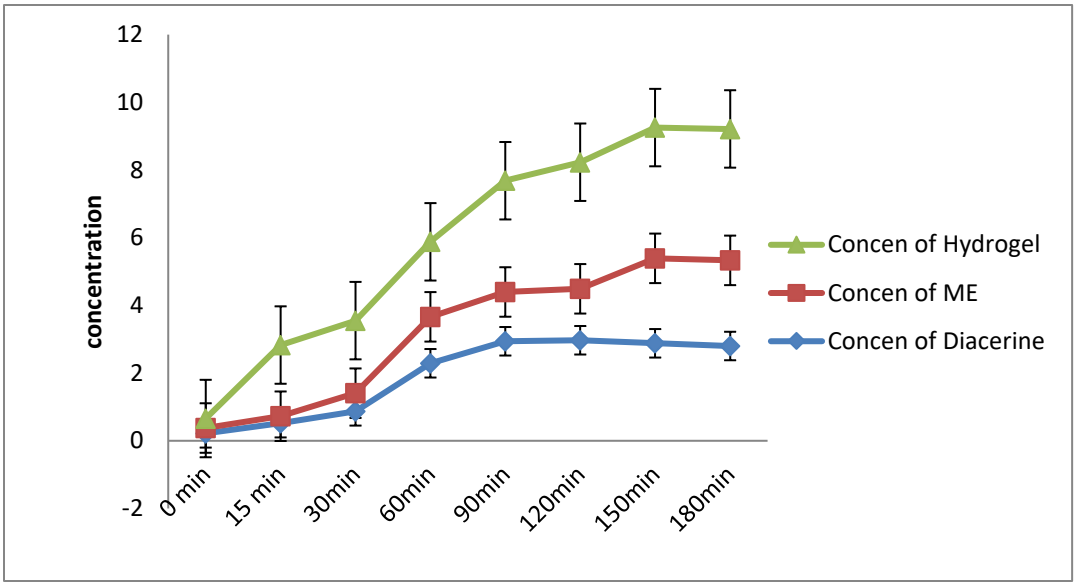

Fig.2- *In -vitro* drug release studies of Diacerine, ME, and Hydrogels (MBH) in Phosphate buffer saline 6.5 pH at 251nm. In-vitro drug release studies of formulations were stated as mean S±D.

Stability Study

At room temperature according to ICH criteria, stability studies were conducted, and the results demonstrated that the formulation remained stable for 3months. The outcomes are illustrated in Table 5.

Table no 5:Various evaluation parameters of MBH

Observations	**Results**
% Transmittance	93.6%
Globule size	20.98nm
Zeta potential	-5.55mv
Viscosity	7615±12.35
pH	5.9 pH
Spreadability (g.cm/sec)	4.2±0.2
Washability	Washable
Homogeneity	No Lump
Drug Content in Microemulsion based Hydrogel	91.80±0.110%

*Mean±SD ; n=3

Table 4: *In vitro* drug release studies of Diacerine, ME and MBH

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Time (min)	Conc of Diacerine (µg/ml)	Conc of ME (µg/ml)	Conc of MBH (µg/ml)
0 min	0.22	0.157	0.28
15 min	0.52	0.205	2.103
30min	0.87	0.536	2.144
60min	2.29	1.372	2.216
90min	2.94	1.456	3.287
120min	2.97	1.52	3.74
150min	2.88	2.51	3.863
180min	2.8	2.53	3.883

Table no 5: Stability studies of MBH as per ICH guidelines

S.no	Temperature ℃	Time interval (month)	Drug Content	Globule size
1	4°C (Refrigerator)	1	91.80±0.112%	20.98 ±0.11nm
		2	91.54±0.120%	20.95 ±0.12nm
		3	91.30±0.125%	20.94 ±0.12nm
2	RT	1	91.80±0.108%	20.67 ±0.21nm
		2	91.50±0.115%	20.58 ±0.31nm
		3	91.33±0.125%	20.34 ±0.44nm
3	45°C Incubator	1	91.44±0.23%	20.98 ±0.65nm
		2	90.52±0.124%	21.88 ±0.67nm
		3	90.10±0.134%	21.98 ±0.11nm

*Mean± SD; n=3

STATISTICAL ANALYSIS

One-way ANOVA was utilized to evaluate the data collected for different formulations. When the P value was < 0.05, the values were deemed statistically significant. According to Table No. 5, P value for all responses for the linear model had been less than 0.05. As a result, the outcomes are deemed noteworthy.

CONCLUSION

The research concluded that ME may be used for the improvement of the solubility and release of the drug diacerine. MBHs were successfully prepared with diacerine (1.5%) as a gelling agent for imparting viscosity to the formulation and also to maintain the drug effect by prolonging the residence time. The viscosity, spreadability, drug content, as well as drug release of the prepared MBH were assessed. The drug release of diacerine achieved from

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MBHs up to 6 h was better drug release, demonstrating drug enhancement of drug release using MBHs. The globule size and drug content of MBHs did not alter throughout three months of stability testing. Consequently, at room temperature, it was discovered that the produced MBH remained stable for 3months.

In conclusion, the MBH of diacerine had been successfully formulated for maintaining the effect of the drug as well as to improve its poor solubility and further can be used to treat osteoarthritis.

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Conflict Of Interest

None

List of Abbreviations

ME= Microemulsion
MBHs=Microemulsion based hydrogel
NSAIDs= Non Steroidal Analgesic Inflammatory Drugs
g/mol= Gram per molar
L/h= Liter per hour
rpm= Rotation per minute
nm= Nanometer
cps= Cycle per seconds
min= Minutes

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