RESEARCH ARTICLE

Microemulgel-based Hydrogel of Diclofenac Sodium using *Lipidium sativum* as a Gelling Agent

Minal Sonule[1], Lalchand D Devhare[*2], M Niranjan Babu[3], Sachinkumar D Gunjal[4], S Varalaxmi[5]

[1]*Nagpur College of Pharmacy, Nagpur, Maharashtra, India.*
[2]*Manwatkar College of Pharmacy, Chandrapur, Maharashtra, India.*
[3]*Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh, India.*
[4]*Amrutvahini College of Pharmacy, Sangamner, Savitribai Phule Pune University, Pune, Maharashtra, India.*
[5]*MB school of Pharmaceutical sciences, (Erstwhile: Sree Vidyanikethan College of Pharmacy) MB University, Tirupati, Andhra Pradesh, India.*

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ABSTRACT

Aim was to prepare hydrogel containing diclofenac sodium using *Lipidium sativum* as a gelling agent within a micro emulsion-based system. The oil phase consisted of soybean oil, while surfactants, namely Span 80 and Tween 20, were employed in the formulation. Absolute ethanol was used as a co-surfactant and were characterized by a phase diagram. The *in-vitro* permeation information is derived from the Franz diffusion. Different microemulsion was designed by screening of various components by performing pseudo-ternary phase diagram and then a solubility study. From this psudo-ternary phase diagram was constructed. *In-vitro* permeation data was screened from these results the topical delivery of diclofenac sodium microemulsion was clearly confirmed as being by means of w/o microemulsion systems. The optimized formulation of the microemulsion consist of soya bean oil 1.25 mL, span:Tween 20 : 2.5 mL, ethanol 1-mL, water 0.2 mL, *L. sativum* mucilage and it is compared with the marketed preparation. So, the micro emulsion-based hydrogel of diclofenac using *L. sativum* mucilage can be used as a gelling agent for a topical drug delivery system.

Keywords: Micro emulsion-based gel, Topical skin delivery, *Lipidium sativum,* Diclofenac.

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INTRODUCTION

Microemulsions represent transparent, stable, and uniform blends composed of oil, water, and a surfactant (S), often complemented by a co-surfactant (CoS). Currently, microemulsions have shown promise in protecting sensitive drugs, controlling drug release, enhancing drug solubility, and reducing variability in patient responses. Furthermore, they have demonstrated their versatility in formulating preparations suitable for various modes of administration. Plentiful studies proved that microemulsion formulations exhibit superior transdermal and dermal delivery properties.[1]

This investigation employed Tween 20 and Span 80, non-ionic surfactants known for their compatibility with the three other surfactant classes and their adaptability across a wide pH range, owing to their minimal toxicity. Given that *Lipidium sativum* served as the gelling agent in this study, the primary focus was on assessing the *in-vitro* release of microemulsion (M) formulations.[2]

To elucidate the relationship between a mixture's composition and its phase behavior, a phase diagram proved valuable. In the context of basic microemulsion systems comprising oil, water, and surfactant, a ternary phase diagram, where each vertex represents 100% of a particular component, was employed to investigate phase behavior. However, in the realm of pharmaceutical applications, it is common for microemulsions to incorporate additional components like co-surfactants and surfactants.[3]

In this study, a microemulsion-based hydrogel was formulated using *L. sativum* as the gelling agent, and a comprehensive analysis of its physicochemical properties was

*Author for Correspondence: lalchand.devhare@gmail.com

conducted. Furthermore, the research encompassed an evaluation of *in-vitro* drug permeation using a Franz diffusion cell.[4]

This study holds particular significance as no prior research has explored the use of *L. sativum* as a gelling agent in microemulsion-based hydrogels and compared it with commercially available preparations. The findings from this study could offer valuable insights into the potential utilization of *L. sativum* in topical formulations.[5,6]

MATERIALS AND METHOD

Diclofenac procured from Zim Ltd Kalmeshwar Nagpur. Carbopol 980 was purchased from Loba chem. All other compounds were of the reagent grade and were utilized directly.

Microemulsion

Preparation of water/oil microemulsions

In this study, Span 80 and Tween 20 were employed as surfactants, while soybean oil was chosen as the oil phase. Pure ethanol was utilized as the co-surfactant. The creation of phase diagrams involved titrating various mixtures of surfactant (S) and co-surfactant (CoS) with distilled water to delineate the regions where microemulsions (M) form. By varying the weight ratios of S and CoS, the boundaries of the M domains were established. The hydrophilic-lipophilic balance (HLB) value was determined to be 5.44, and two different S/CoS weight ratios, namely 1:1 and 9:1, were examined.

To prepare the microemulsion, the surfactants were first mixed, heated, and then added to the appropriate amount of soybean oil, followed by blending and melting at 60°C. This mixture was supplemented with the co-surfactant, and the formulation process involved gradual titration with distilled water. The liquid was stirred using a magnetic stirrer and a stirring bar until turbidity became evident. A phase diagram was instrumental in identifying the optimal S/CoS weight ratios and the regions where microemulsions could be formed.

Psudoternary phase diagram

This involved gradually introducing water into a transparent mixture of oil and surfactant/co-surfactant (S/CoS) solutions to create the pseudo-ternary phase diagram. Each phase diagram maintained a fixed oil-to-mixture ratio of 1:1, while the specific weight ratios of surfactant and co-surfactant varied.

Table 1: Composition of pseudo ternary phase diagram

S. No	*%w/v of oil*	*%w/v of s/cos*	*%w/v of water*
1	87.80	9.75	2.43
2	76.92	19.23	3.84
3	66.66	28.57	4.76
4	55.81	37.20	6.97
5	45.45	45.45	9.09
6	36.36	54.54	9.09
7	26.08	60.86	13
8	16.66	66.86	16.66
9	8.33	72	20

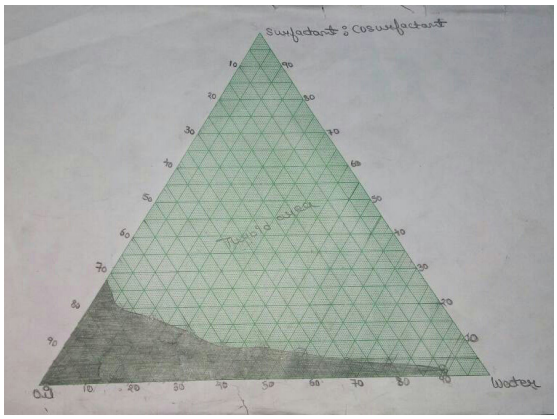

Figure 1: Pseudoternary phase diagram

During this process, water was added drop by drop from a burette to the mix of oil, surfactant, and co-surfactant under moderate manual agitation. After allowing time for equilibration, the mixtures were visually inspected to distinguish between microemulsions (clear) and crude emulsions (turbid) based on their clarity. The transition from a clear solution to turbidity marked the point of detection.

To create the phase diagrams, a practical approach involved drawing water dilution lines that illustrated an increase in water content while decreasing the S/CoS ratio. Water was incrementally added along these lines, starting from the apex representing 100% S/CoS and progressing towards the oil side of the triangle. Composition of pseudo ternary phase diagram is shown in Table 1 and Figure 1.

Formulation of drug loaded micro emulsion

According to the microemulsion regions in the phase diagram, formulations were selected. Drug loading was carried out by combining the medication with a clear microemulsion made of water, oil, surfactants, and co-surfactants. Extra medication was added and ultrasonically mixed with the transparent microemulsion in a stopper vial. Equilibrated samples were taken out of the shaker and centrifuged at 3000 rpm for 15 minutes. Supernatant removed and filtered. Content of diclofenac sodium was identified using UV spectrophotometer at 276 nm.

Selection of M formulations for further studies

Microemulsions selected for further investigation were taken from the central region of the M formation area. These chosen samples were subjected to various tests, including assessments of visual clarity, conductivity, centrifugation, and pH levels.

- *Visual clarity*

All the formulation (M1, M2) were inspected visually for clarity against a white background.

- *Conductivity Measurements*

The prepared microemulsion is confirmed to be water in oil microemulsion by measuring their electrical conductivities using a conductivity meter.

• *Centrifugation*

Physical stability was studied using centrifugation at 13,000 rpm for 30 minutes. After centrifugation, the samples were observed for clarity and any phase separation.

Formulation of microemulsion-based hydrogel

In order to enhance the viscosity and applicability of formulated microemulsion; it further converted hydrogel. For this purpose, *L. sativum* gel is used as a hydrogel. The gel matrix was prepared simply by allowing the gelling agent to swell in water for 24 hours. Stability and gelling capacity was adjusted for its pH. The pH was brought down to the range of 7 pH with the addition of tri-ethanolamine. The composition of the microemulsion is given in Table 2.

Conversion of microemulsion in microemulsion-based hydrogel

Microemulsion was converted into microemulsion hydrogel by the addition of the gel matrix to the microemulsion formulation with the help of stirring with a mechanical stirrer for 10 minutes.

Categorization of microemulsion-based hydrogel

• *Physical examination*

Prepared microemulsion hydrogel formulation was assessed visually.

• *In-vitro release and permeation studies*

Were conducted using a Franz diffusion cell. The investigation into the *in-vitro* drug release of emulgel formulations involved the use of a Franz diffusion cell along with a dialysis membrane. The dialysis membrane was first treated with sodium hydroxide and soaked overnight in a phosphate buffer solution with a pH of 7.0 while being kept at a low temperature. This treated dialysis membrane was then placed between the donor and receptor compartments of the Franz diffusion cell.

A quantity of 0.5 grams of the microemulsion hydrogel formulation was applied onto the dialysis membrane. To ensure that the diffusion layer effect did not interfere, a magnetic bar was utilized to maintain continuous stirring of the diffusion medium. Samples were collected and subsequently analyzed using a UV spectrophotometer.

• *Rheological studies*

The viscosity of various microemulsion hydrogel formulations was assessed at 25°C. A beaker with a thermostatic jacket on it received the formulation whose viscosity was to be measured. The spindle was given free rein inside the hydrogel microemulsion and the reading was recorded.

• *Spreading coefficient*

A microemulsion hydrogel must also have strong spreadability in order to satisfy the requirement of the optimal amount. When measuring the spreadability of emulgel and commercial gels, the diameter of the emulgel circle formed when the gel was sandwiched between two glass plates of a specific weight was used. A glass plate weighed out at 350 mg of emulgel or gel was placed on it, and another glass plate was dropped onto it from a distance of 5 cm. A measurement was made of the spread emulgel circle's diameter.

Table 2: Composition of microemulsion

S. No.	*Ingredient*	*Quantity*	
		M1	*M2*
1	Soyabean oil	1.25 mL	1.25 mL
2	Span 80:tween 20	2.5 mL	2.5 mL
3	Ethanol	1 mL	1 mL
4	Water	0.2 mL	0.2 mL
5	*L. sativum* gel	1 g	2g

• *Extrudability studies of topical microemulsion hydrogel*

It was conducted using the tube test, typically involving the measurement of the force required to expel the material from the tube.

The assessment is made by applying a specific weight in grams needed to extrude a minimum of 0.5 cm of the microemulsion-based hydrogel within a 10-second timeframe. A higher extrudability score indicates a greater amount of material being successfully extruded.

The extrudability of each formulation is assessed three times, and the results are averaged. To quantify extrudability, the following formula is applied:

Extrudability = Weight applied to extrude the microemulsion-based hydrogel from the tube in grams per centimeter.

• *Drug content determination*

It involved taking 1-gram of the hydrogel microemulsion and mixing it with an appropriate solvent. This mixture was then filtered to obtain a clear solution. The absorbance of the solution was measured using a UV spectrophotometer.

• *pH*

It was determined by dissolving 1-gram of gel in 100 mL of distilled water and allowing it to stand for two hours. The pH measurements were carried out using a digital pH meter, with each formulation being tested three times, and the average readings were computed.

• *Skin irritation test (Patch Test)*

Preparation carefully applied to the skin of human volunteers. Any adverse effects, such as changes in skin color, were monitored for up to 6 hours. This test was conducted with a total of 8 human volunteers, and it was considered successful if no skin irritation occurred. If skin irritation symptoms were observed in more than two individuals, the test was repeated.

Stability studies

It involved placing the produced microemulsion-based hydrogel into aluminum collapsible tubes (5 g) and allowing it to stabilize in an atmospheric environment for a month. At 15-day intervals, samples were withdrawn, and the pH and medication concentration were assessed.

Table 3: Composition of microemulsion

S. No	*Ingredient*	*Quantity*	
		M1	*M2*
1	Soyabean oil (mL)	1.25	1.25
2	Span 80:Tween 20 (mL)	2.5	2.5
3	Ethanol (mL)	1	1
4	Water (mL)	0.2	0.2
5	*L. sativum* gel	1G	2G
6	Diclofenac sodium	0.116G	0.116G

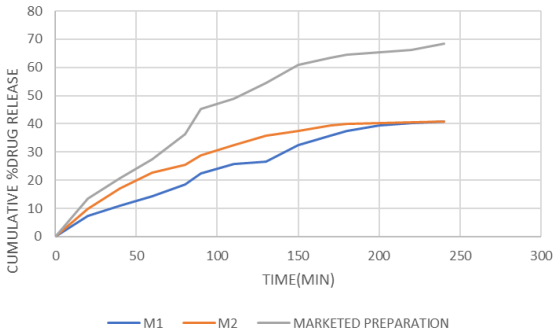

Figure 2: Permeation profile of diclofenac microemulsion-based hydrogel through dialysis membrane

RESULT AND DISCUSSION

Formulation of Micro Emulsion-based Hydrogel

Formulation of gel matrix

After the successful formulation and assessment of microemulsion, the challenge was to bring it into topical applicable form. To convert it into hydrogel-based formulation gel matrix was formed considering *L. sativum* mucilage as shown in Table 3.

In-vitro release study of micro emulsion based gel with penetration enhancer

At the end of four hours, the percentage cumulative medication release of all the generated formulations (M1, M2) is graphically depicted in Figure 2. When compared to the commercially available preparation, the formulation M2 showed maximum drug release, while the formulation M1 showed minimal drug release. The larger concentration of the gelling agent is blamed for the higher release.

Rheological study

The viscosity of all the prepared microemulsion-based hydrogel is shown in Figure 3. The result showed that the microemulsion-based hydrogel of M1 formulation showed 1400 centipose as compared to the M2 formulation. The voveron emulgel formulation was found to be 1450.

Spreading coefficient

The spreadibility value of all the prepared microemulsion-based hydrogel was depicted in Figure 4. The highest spreading coefficient was found M2 formulation. The spreading depends upon the viscosity so its increases as the viscosity decreases concluding that the formulation spreads well.

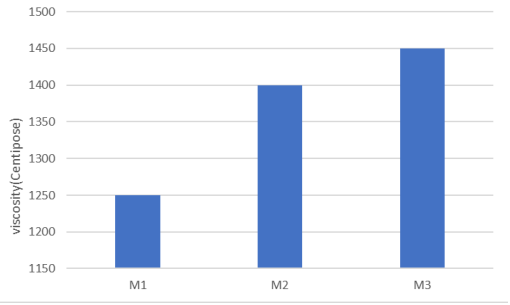

Figure 3: Viscosity of micro emulsion-based hydrogel

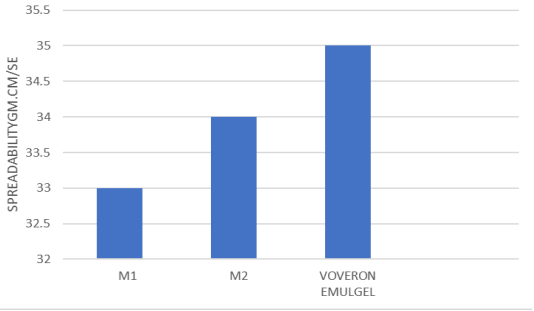

Figure 4: Spreadability of microemulsion-based hydrogel

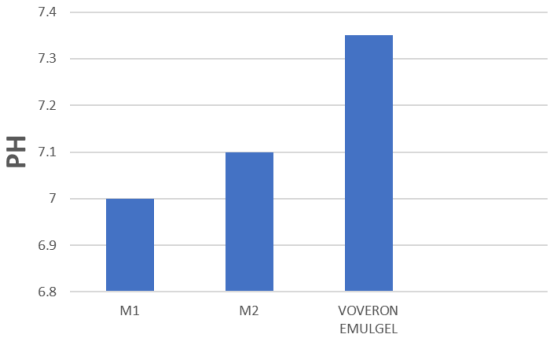

Figure 5: pH of the microemulsion-based hydrogel

pH formulation

The pH value of the formulation is given in the table. M1, M2 are lie in the normal range of pH. which is also shown in Figure 5.

Extrudability

The results show that a greater amount of microemulsion-based hydrogel extrudes at low pressure from the tube, improving patient compliance and demonstrating the extrudability of emulgel.

Drug content determination

The amount of medication in the emulgel suggested that the system was suitable for high trapping in the internal phase

Measurement of pH

The pH of the microemulsion-based hydrogel was in a normal range of skin.

- *Skin irritation test*

No allergic reactions appeared on humans at 6 hours test.

- *Stability study*

All prepared microemulsion-based hydrogel were found to be stable upon storage, no change was observed.

DISCUSSION

This study examined diverse microemulsion systems as a budding vehicle for topically drug delivery systems. Different microemulsions were designed by screening of various components by performing a pseudo-ternary phase diagram and then a solubility study. Soyabean oil was chosen as the oil phase, span 80: Tween 20 was used as the surfactant in that ratio 9:1. and co-surfactant ethanol, respectively. From these pseudo-ternary phase diagrams were constructed. *In-vitro* permeation data was screened. From these result the topical delivery of diclofenac sodium microemulsion was clearly confirmed as being by means of w/o microemulsion systems. The optimized formulation of the micro emulsion consist of soya bean oil 1.25 mL, span :Tween 20 2.5 mL, ethanol 1-mL, water 0.2 mL, *L. sativum* mucilage. After the screening of microemulsion formulation with stable and high permeation enhancing characteristics, the *L. sativum* gel was prepared in which we used carpool and *L. sativum* as a gelling agent, n- metabisulphite and n-methylparaben as a preservative. pH, drug content and *in-vitro* release study were carried out.

CONCLUSION

Based on the findings from the aforementioned study, it can be concluded that a microemulsion-based hydrogel was successfully formulated using *L. sativum* mucilage as the gelling agent.[7,8] This formulation underwent a series of physicochemical studies, rheological assessments, spreadability evaluations, and *in-vitro* release investigations. Among these *in-vitro* studies, it was observed that formulation M2 exhibited the highest level of drug release. To further assess its performance, formulation M2 was compared to a commercially available preparation.[9-11]

The results indicate that the microemulsion-based hydrogel utilizing *L. sativum* mucilage as a gelling agent has the potential to serve as an effective vehicle for topical drug delivery systems.[12-14] These findings highlight the promise of this formulation for enhanced drug release and suggest its suitability for use in topical applications.

REFERENCES

1. Williams HD, Trevaskis NL, Charman SA. Strategies to address low drug solubility in discovery and development. Pharmacological Reviews 2013;65(1):315-499.
2. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Advanced Drug Delivery Reviews 2002;54 (Supplement): S77-S98.
3. Singh Y, Meher JG, Raval K. Microemulsion: A novel approach to enhance drug solubility." Recent Patents on Drug Delivery & Formulation 2017;11(1):47-60.
4. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Advanced Drug Delivery Reviews 2012; 64:175-193.
5. Devhare LD and Gokhale N. Antioxidant and antiulcer property of different solvent extracts of cassia tora linn. Research journal of pharmacy and technology. 2022;15(3):1109-1113.
6. Solans C, Solé I. Nano-emulsions: Formation by low-energy methods. Current Opinion in Colloid & Interface Science 2012;17(5):246-254.
7. Akhtar N, Sharma JK, Shams MZ. Microemulsion as a novel approach for transdermal drug delivery: A comprehensive review. Current Drug Delivery 2020; 17(7):558-576.
8. Fang JY, Fang YP, Chiu WT. Effects of lipophilic emulsifiers on the percutaneous absorption of capsaicin from hydrogels. International Journal of Pharmaceutics 2006; 311(1-2):19-26.
9. Sarwar M, Javadzadeh Y, Jafari-Navimipour B. An overview of the different excipients used in the development of microemulsion drug delivery system. Reviews in Pharmaceutical Sciences 2014;1(1):43-50.
10. Adimulapu AK, Devhare LD, Patil A, Chachda NO, Dharmamoorthy G. Design and Development of Novel Mini Tablet Cap Technology for the Treatment of Cardiovascular Diseases. International Journal of Drug Delivery Technology. 2023;13(3):801-806.
11. Trivedi R, Rajalakshmi R, Srivastava. Microemulsion: As an advanced drug delivery system. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2016; 7(3):2869-2880.
12. P N Chougule, K Koumaravelou, NB Chougule. Fabrication, Optimization and Evaluation of Escin
13. Enriched Emulgel System for Treatment of Varicose Veins. International Journal of Drug Delivery Technology. 2023;13(3):833-841.
14. Williams AC, Barry BW. Penetration enhancers. Advanced Drug Delivery Reviews 2004;56(5):603-618.