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Research Article

CAPSAICIN EMULGEL- DESIGN, OPTIMIZATION AND FORMULATION FOR TOPICAL DELIVERY

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ABSTRACT

Topical therapy with emulgel -type of products allows efficient delivery of bioactive compounds with additional benefits to patients. This research aimed to design, optimize, formulate, and evaluate in vitro parameters between gels loaded with a microemulsion of extracted capsaicin to their standard. A crude form of capsaicin was extracted from capsicum. Using Box Behnken design, 15 different microemulsions were made by ultrasonication and optimized by varying three independent variables (amount of olive oil, Hydrophilic-lipophilic balance value of surfactants, and amount of surfactants used) using Stagraphic Centurion software. Microemulsions were optimized based on their organoleptic characters; dilution test, centrifugation test and P^H, and gelling agent Carbopol-940 was determined by its viscosity, spreadability, swelling index, consistency, and P^H. Finally, a stable capsaicin emulgel (0.05% and 0.1%) was made by incorporating optimized microemulsion (F8) and optimized gelling agent, 0.6% Carbopol- 940. Those final capsaicin emulgels were tested for drug content percentage, which was within the standard range.

Keywords: Analgesic, capsaicin, capsicum extract, emulgel, microemulsion

INTRODUCTION

Topical drug delivery is an effective, targeted, and popular therapy for local dermatological disorders because it avoids the first-pass effect, gastrointestinal irritation, and metabolic degradation associated with oral administration (Shrestha *et al.*, 2017; Garg *et al.*, 2015). Topical routes provide high therapeutic efficacy along with a more beneficial profile of adverse effects than in regular systematic application, especially for analgesic drugs like lidocaine and capsaicin in patches, capsaicin creams, or emulgels (Leppert *et al.*, 2018). However, most topical drug delivery systems fail to deliver desired therapeutic drug concentration as the body's physiochemical barrier hinders the thermodynamic activity of permeating drug (Loftsson, 2022). A hydrophilic stratum corneum exerts less permeation for the lipophilic drug, but hydration of this layer equally increases the permeability of any drug, and such drug permeation may be affected by physiological factors like thickness, skin layer hydration degree, skin p^H, lipid content, skin follicle densities, and network of blood flows, or by physiochemical factors like partition coefficient, molecular weight, and degree of ionization (Khullar *et al.*, 2012). Irritant capsaicin is mainly found in hot chili peppers (*Capsicum* species) and, when applied topically, is used to treat various diseases such as rheumatoid arthritis, diabetic neuropathy, post-therapeutic neuralgia, and to reduce pain in burning mouth syndrome, Guillain -Barre syndrome, refractory pain, cluster headache, osteoarthritis, and atypical odontalgia (Bhattacharya *et al.*, 2017). Capsaicin, a hydrophobic active, has a typical oral dose of 8-10 mg, and for topical application, the dose ranges from 0.025% - 0.25%. Capsaicin is highly soluble in ethanol (30 mg/ml at least) and olive oil (Reyes-Escogido *et al.*, 2011). Since a major drawback of the topical dosage form is the delivery of hydrophobic drugs, to overcome this limitation, microemulsion containing lipophilic active as internal phase is incorporated with hydrogel to produce microemulgel for enhancing bioavailability (Ashara *et al.*, 2016a; Bhattacharya *et al.*, 2017; Shah *et al.*, 2013; Acharya & Bhatta, 2022).

Microemugel, a monophasic, thermodynamically stable, and optically isotropic colloidal dispersion, provides a large surface area and uniform skin distribution by a thixotropic mechanism that offers potential therapeutic effects to the applied site for any biopharmaceutical classification system of drugs (Jagdale *et al.*, 2020; Vanti *et al.*, 2021). Microemulgel can increase the bioavailability of any drug where the microemulsion's internal lipophilic phase increases skin permeation and gelling agent stabilizes the entire system (Ashara *et al.*, 2016b; Jagdale *et al.*, 2020). The microemulsion is gelled by the gelling agent with appropriate vehicle that enables poorly permeable drugs to have longer therapeutic residence time on the target site , reducing application frequency and increasing product efficacy (Torregrosa *et al.*, 2020). Therefore, this research was conducted to prepare stable microemulgel of hydrophobic capsaicin samples obtained from the market and isolated in our laboratory.

MATERIAL AND METHODS

Extraction of capsaicin

Red capsicum fruits were collected from a different area of Kavre, Nepal, and dried for 24 hours in a hot air oven at 50°C. It was grinded repeatedly until it turned into fine powder that passed through mesh size of 50 mm and was macerated on ethyl acetate for 48 hours. It was then filtered and concentrated on a rotatory evaporator and vacuum controller (R-215, V-850). Crude capsicum extract was mixed with 1.5 g of silica gel (Merck, 60-120 mesh) and loaded on top of a chromatographic column (90x8 cm) packed with dry silica gel (120 mesh) for fractionation. Petroleum ether, benzene, ethyl acetate, and ethanol were used as gradient solvents for elution. These different fractions were collected, labelled, and pooled based on visual color separation. Aliquots from each fraction were scanned with UV spectrophotometer (Shimadzu UV-01800) to confirm the capsaicin peak, and the confirmed elution pool was again concentrated on a rotatory evaporator and vacuum controller (Buchi, R-215, V-850) to produce a yellowish-brown residue that turned into dark brown solid in further storage at 2.5 °C on the refrigerator. Extracted capsaicin purity was calculated by making 40µg/mL in ethanol, and absorbance was seen at 280nm on a UV photometer (Shimadzu UV-01800).

A B C

Figure 1. Column chromatography on the extraction of capsaicin (A). Fractions of column eluents (B). Solvent evaporation on rotavapour (C).

Table 1. Design parameters for emulsion.

Independent factors	Levels		
	-1	**0**	**+1**
HLB Value of S_{mix}	6.8	7.5	8.3
Amount of Surfactant	2 %	5 %	8 %
Amount of Olive oil	4 %	6 %	8 %

Table 2. BBD design for micro-emulsion formulations.

Formulation	Span 40(%)	Polyethyleneglycol (PEG) 400 (%)	$S_{mix(\%)}$	Oil (%)	HLB value
F1	3.50	1.50	5.00	6.00	8.30
F2	4.20	0.80	5.00	6.00	7.50
F3	1.68	0.32	2.00	4.00	7.50
F4	4.20	0.80	5.00	6.00	7.50
F5	7.84	0.16	8.00	6.00	6.80
F6	3.50	1.50	5.00	6.00	8.30
F7	6.72	1.28	8.00	6.00	7.50
F8	1.40	0.60	2.00	4.00	8.11
F9	1.68	0.32	2.00	6.00	7.50
F10	6.72	1.28	8.00	8.00	7.50
F11	5.60	2.40	8.00	8.00	8.30
F12	4.90	0.10	5.00	4.00	6.80
F13	1.96	0.04	2.00	8.00	6.80
F14	4.20	0.80	5.00	8.00	7.50
F15	4.90	0.10	5.00	4.00	6.80

BBD (Box Behnken Design) for microemulsion development

15 different formulations were designed, prepared, and studied by varying amounts of olive oil, Hydrophilic-lipophilic balance (HLB) value of surfactants, and amount of surfactants using Statgraphic Centurion software version 19 at three levels, as shown in Table 1 and Table 2.Span 40% was a major emulsifier (surfactant) that affected the co-sufactant PEG 400, on overall emulsion HLB value ranging from 6.8 – 8.3.

Solubility screening of capsaicin on selected excipients

Capsaicin is more soluble in olive oil than other available fixed oils like almond oil, and sunflower oil (Reyes-Escogido *et al.*, 2011). To optimize the skin penetration effects of capsaicin, olive oil was selected as a solvent. we chose PG, olive oil and PEG as availability in our lab, where 1mg of capsaicin dissolved in 1ml of each such solvents and its remaining residue observed visually, and solubility concluded showing that olive oil showed best solubility at 30mg capsaicin completely dissolved in 1ml olive oil whereas PEG 400 showed least solubility capacity means 2.5 mg capsaicin in 1ml PEG 400.

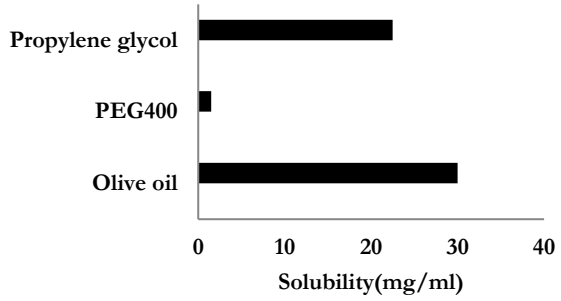

Figure 2. Solubility screening of capsaicin in oil phase

Preparation of base microemulsion

Oil phases were prepared by BBD suggested amount of span 40 and olive oil with 0.4% Butylated hydroxytoluene (BHT) at 70 °C. Water phases were prepared by BBD's suggested amount of PEG 400, 8% propylene glycol, 0.3% menthol, 0.15% methyl parabens, and 5% ethanol in distilled water at 70 °C. Now oil phase was added to the water phase with continuous stirring and then sonicated by ultrasonication (Microson ultrasonic cell distributor) for 45 seconds.

Characterization of microemulsion for optimization

Organoleptic characters

Physical appearance and creaming in 24 hours of microemulsions (F1-F15) were performed visually and graded, respectively.

Dilution test

1ml of the emulsion was taken in a volumetric flask, and the addition of 9 ml of distilled water was done for 1:10 dilution and observed visually for cracking of the system. Similarly, a further 90 ml of continuous phase was added to all samples loaded in volumetric flasks for 1:100 dilution, and cracking of systems was observed and graded according to the previously described method (Godbole *et al.*, 2018).

pH

All preparation was observed in calibrated HI 2210 pH meter (HI 2210 pH meter) at 25 °C (Godbole *et al.*, 2018).

Viscosity and Flowability

A spindle of 64 was used at 1,2and 3 rpm to measure the viscosity with Brookfield Viscometer (DV III Ultra). The flowability of different samples was observed and graded, respectively (Khullar *et al.*, 2012).

Table 3. Emulsion response variable grading.

Parameters	Poor	Fair	Good	Very good	Better
Creaming in 24 hrs	5	10	15	20	25
Dilution	5	10	20	30	40
Flowability	0	1	2	3	4

Forced Creaming

10 ml of each microemulsion was subjected to centrifugation for 10 minutes at 5000 RPM to observe forced creaming percentage, and calculated as described (Ashara *et al.*, 2016a).

$$Creaming\ percentage = \frac{height\ of\ cream\ after\ centrifugation}{Initial\ volume\ of\ emulsion} \times 100\%$$

Microscopic property

A Sudan-H red dye was used for confirmation of o/w microemulsion on an optical microscope (100x).

Characterization of gelling agent

Development of gel

The carbopol-940 solutions of 0.2%, 0.4%, 0.6%, 1%, 1.5%,2%, 3%, 4%, and 5% were made in warm distilled

water, and final volume was made up to 100 ml with continuous stirring. Triethanolamine was added dropwise to maintain pH between 5.5-7. The prepared gels were allowed to stand for the next 24 hours for complete swelling and were graded visually based on their viscosity and turbidity after 24 hours of gel preparation.

Swelling index(SI)

One gram of carbopol-940 was placed on a measuring cylinder, and 100ml of distilled water was added with the addition of 10 ml of 0.1 M NaOH in it. Final results were observed after 24 hours of gel preparation and calculated by following Pakhare *et al.* (2017). This process was repeated three times (n=3).

$$SI = \frac{V24 - V0}{V0} \times 100\%$$

Where, V_{24} = swelling volume of the gel after 24 hours
V_0 = initial volume of gel

Spreadibility

Spreadibility was determined by placing 0.10 grams of gel in between two Petri plates and providing a pressure of 125 grams for 1 minute. Uniform manual force was given to separate such plates, and time taken to separate such plates was noted along their maximum and minimum diameter spread on both upper plate and lower plate (Ashara *et al.*, 2016a).

Development of capsaicin emulgels and characterization

Preparation of capsaicin emulgels

Optimized carbopol-940 concentration was incorporated into optimized microemulsion for preparation of emulgel. Optimized carbopol-940 for 50 grams was prepared, adjusted pH to 6.5 by triethanolamine, and allowed to stay overnight. Now, separate microemulsions were prepared by dissolving 0.05-gram standard capsaicin and 0.10 gram extracted capsaicin in BBD-adjusted olive oil concentration. Oil phases were prepared by heating the suggested amount of span 40 with 0.4% BHT at 70 ^{o}C. Water phases were prepared by heating the suggested amount of PEG 400, 8% propylene glycol, and 0.15 % methyl parabens in distilled water at 70 ^{o}C. Oil phase was added to water phase slowly with continuous stirring, with addition of 0.3% menthol and 5% ethanol, then sonicated for 45 seconds for preparation of stable microemulsion. These 50 grams separately prepared microemulsions were added to 50 grams of pH maintained Carbopol-940 at rpm 2500 with electric stirring Remi Lab stirrer (RQ-121/D).

Physiochemical parameters

The clarity and appearance of gels were evaluated visually. Spreadability, viscosity, and pH were determined as described previously (Godbole *et al.*, 2018).

Drug content analysis

Both 0.05% standard capsaicin emulgel and 0.1% extracted capsaicin emulgel were made at 50 µg/mL by dilution with ethanol, and absorbances were measured at 280 nm on UV photometer (Shimadzu UV-01800). Triplicate absorbances were taken (n=3). Their absorbances were compared with standard capsaicin powder using already established linear equation Y= 0.0155x -0.0338 (Acharya & Bhatta, 2022) where standard 100% purity capsaicin powder showed absorbance of 0.735±0.567 at 280 nm in Shimadzu UV-01800.

The % assay was calculated as;

$$\%assay = \frac{(\text{sample absorbance} \times \text{standard concentration})}{(\text{standard absorbance} \times \text{sample concentration})} \times 100\%$$

Blank & Placebo-interference

Blank solution Ethanol (95% purity) peaks were scanned at 200nm - 600nm. Similarly, Placebo emulgel was prepared without loading capsaicin in already weighted excipients according as shown in table 6, and it was developed with ethanol (95% purity) at 50 µg/mL to see any peaks of interference by excipients, scanned them at 200 nm – 600 nm.

Statistical Analysis

Data were analyzed by SPSS 16.0.0. Equations to estimate correlation coefficient (R^2) value were obtained by the already developed linear method (Acharya & Bhatta, 2022).

RESULTS AND DISCUSSION

Purity of extracted capsaicin

It was found that from the 582.7300 gram of powdered *capsicum* fruits, a total of 9.8588 grams of crude dry capsaicin were collected. The (mean± standard deviation) (n=3) absorbance of capsaicin at 40 µg/mL extracted, and absorbance of standard capsaicin were 0.545±0.120 and 0.555±0.450, respectively. It is confirmed that the extracted capsaicin had 98.20% purity using already developed linear method when compared with the standard sample (Acharya & Bhatta, 2022).

Optimization of microemulsion

Organoleptic characters, dilution test, viscosity, Forced creaming, and pH

All formulations had an acceptable pH value (Pakhare *et al.*, 2017). However, F4, F6, and F8 had a smaller % of forced creaming. From table 4, F8 had a low value for creaming in 24 hours, a high value for dilution capacity, and a high value for flowability (Godbole *et al.*, 2018). Hence, F8 showed the most desirable property, close to stable micro-emulsion (RHLB~7) (Ashara *et al.*, 2016a), and was chosen for loading into gelling agent Carbopol 940.

Table 4. Results for optimization of micro emulsions (F1-F15).

Formulation	Physical appearance	Dilution	Creaming in 24 hours	Flowability	PH	Forced Creaming
F1	Milky yellowish	40	5	3	7.03	8.66
F2	Milky	20	5	2	6.92	23.33
F3	Milky	40	10	3	6.88	16.66
F4	Milky	40	5	3	7.04	6.33
F5	Milky yellowish	30	20	3	7.11	8.21
F6	Milky	40	5	3	6.90	6.66
F7	Milky	10	25	4	6.98	7.09
F8	Milky	40	5	4	7.18	6.66
F9	Milky	40	20	2	6.90	7.66
F10	Milky	5	25	0	7.00	100.00
F11	Milky	5	25	0	6.03	100.00
F12	Milky	5	25	0	6.99	100.00
F13	Milky	40	5	3	6.73	17.00
F14	Milky	5	25	0	6.14	100.00
F15	Milky	40	10	4	6.78	14.00

.

A B

Figure 3. Forced creaming percentage is less for F8 (A) and high for F11 (B).

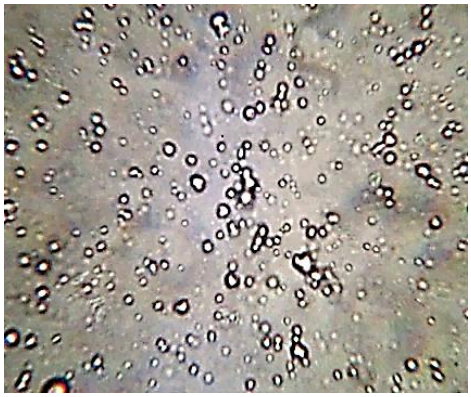

Figure 4. Optimized micro-emulsion (F8) under an optical microscope (100x).

Table 5. Organoleptic characters for different concentrations of Carbopol-940.

Concentration (%)	Viscosity	Turbidity	pH	SI	Spreadability	
					Spreading diameter(cm)	Pull Time(sec)
0.2	Viscous	Somehow transparent	6.46	13.33	4.41	12.66
0.4	Viscous	Somehow transparent	6.34	25.00	4.78	13.66
0.6	Viscous	Somehow transparent	6.30	75.00	5.58	10.66
1.0	More viscous	Somehow transparent	6.35	NC	NC	NC
1.5	Highly viscous	Less transparent	7.00	NC	NC	NC
2.0	Extreme viscous	Less transparent	6.89	NC	NC	NC
3.0	Almost solid mass	Turbid	6.99	NC	NC	NC
4.0	Solid mass	More turbid	7.01	NC	NC	NC
5.0	Solid mass	Extremely turbid	7.00	NC	NC	NC

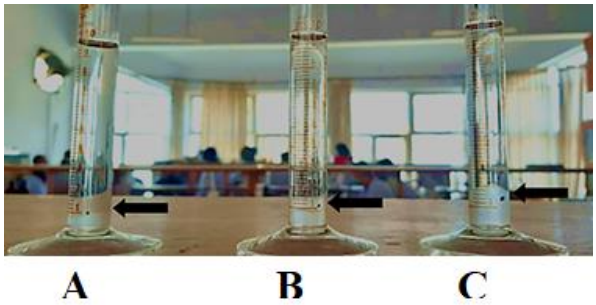

Figure 5. Swelling index of 0.2 % (A), 0.4 % (B), and 0.6 % (C) of carbopol-940.

Microscopic examination of optimized microemulsion

F8 microemulsion red-white oil droplet on water phase was shown in figure 4. This indicates that there is a well formulation of product, and it is incorporated in the base.

Characterization of gelling agent

All carbopol-940 (%) had acceptable pH. However, 0.2%, 0.4%, and 0.6% carbopol-940 study showed desirable visual characteristics and were evaluated only further because concentrations (%) > 0.6% were more viscous, so they were not considered (NC) for further testing as shown in Table 5. 0.6% of carbopol-940 was chosen as it had desirable SI and spreadability (Ashara *et al*., 2016a; Khullar *et al*., 2012).

BBD (Box Behnken Design) for microemulsion development

Multiple response optimizations for micro-emulsions were analyzed by Stat Advisor (shown in Fig. 6), where A = HLB, B = olive oil amount, and C = surfactant amount was considered independent variables, giving that F8 was the best formulation as it showed RHLB value of almost 7.5 which was considered as best (Ashara *et al*., 2016a). Hence, the best formulation for emulgel was emulsion (F8) and 0.6% Carbopol (Table 6).

Characterization of prepared emulgels

Physiochemical parameters

Both formulated capsaicin emulgels had desirable clarity, appearance and had pH 6.49±0.09 and 6.87±0.04 for 0.05% standard capsaicin emulgel and 0.1% extracted capsaicin emulgel, respectively, which were acceptable (Pakharel *et al*., 2017). Both emulgels spreadability laid in acceptable range of 5.00-7.00 cm (Khullar *et al*., 2012) shown in Table 7. Figure 7 explained on increasing RPM (stress) the dial reading had decreased (viscosity decreasing), a non-Newtonian-type flow, requisite characteristics for any topical delivery (Jagdale *et al*., 2020).

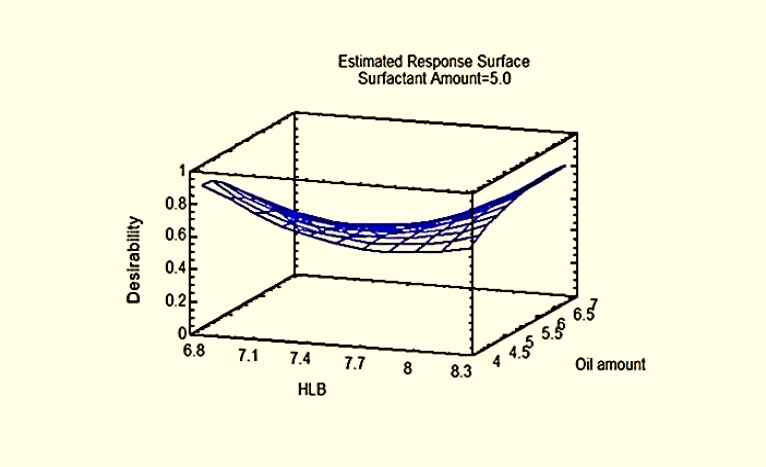

Figure 6. Optimize desirability for microemulsions by Statadvisor.

Table 6. Optimized formulae for capsaicin (0.1% extracted and 0.05% standard) emulgels.

Ingredients(grams)	0.1% extracted capsaicin emulgel	0.05% standard capsaicin emulgel
For 50-gram microemulsion		
Capsaicin	0.10	0.05
Span 40	1.40	1.40
Olive oil	4.00	4.00
BHT	0.40	0.40
PEG 400	0.60	0.60
Propylene Glycol	8.00	8.00
Menthol	0.30	0.30
Methyl parabens	0.15	0.15
Ethanol	5.00	5.00
Distilled water	Qs	Qs
For 50-gram Carbopol -940 gel		
Carbopol-940	0.6	0.6
Distilled water	Qs	Qs

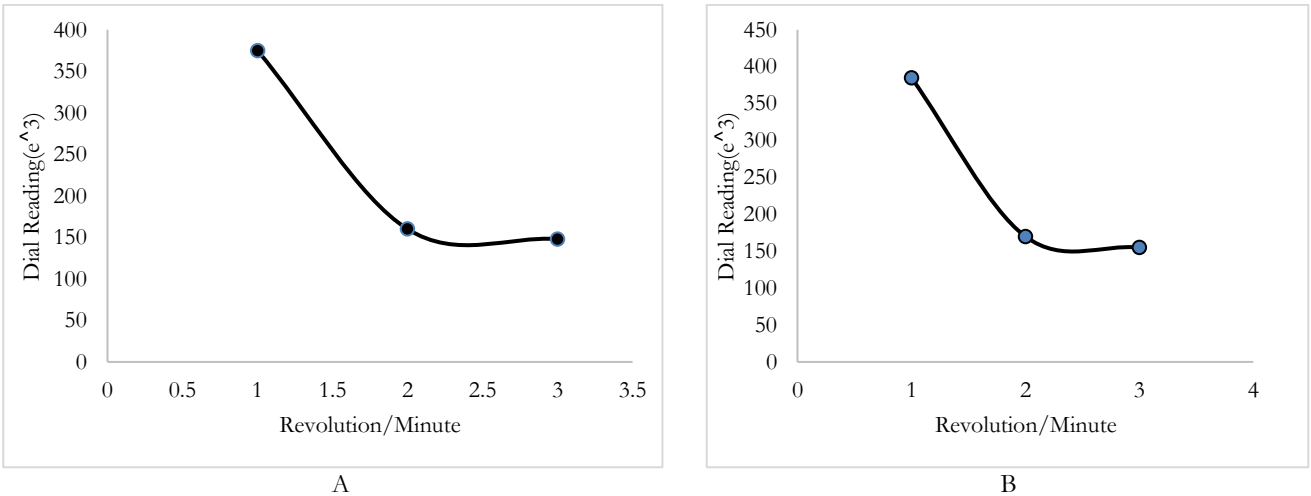

Figure 7. Viscosity showing for capsaicin emulgel (A) 0.05% standard, (B) 0.1% extracted.

Table 7. Desirable spreadability for optimized emulgels.

Diameter (cm) For standard capsaicin emulgel (0.05%)			**Time taken to pull two plates(sec)**
	Maximum	**Minimum**	
Upper plate	5.8	5.3	8, 9, 9
Lower plate	5.7	5.2	
Diameter (CM) For extracted capsaicin emulgel (0.1%)			**Time taken to pull two plates(sec)**
	Maximum	**Minimum**	
Upper plate	5.6	5.3	8, 9, 9
Lower plate	5.7	5.1	

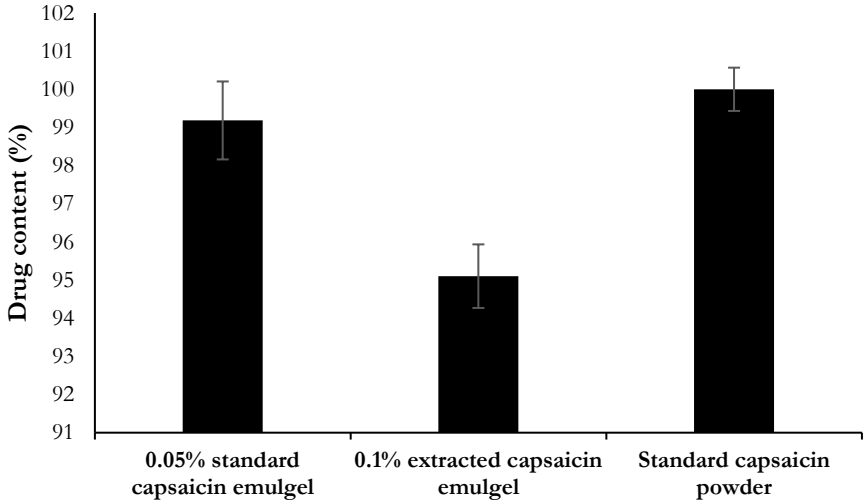

Figure 8. Drug content (%) shown for formulated emulgels in comparison with standard capsaicin powder.

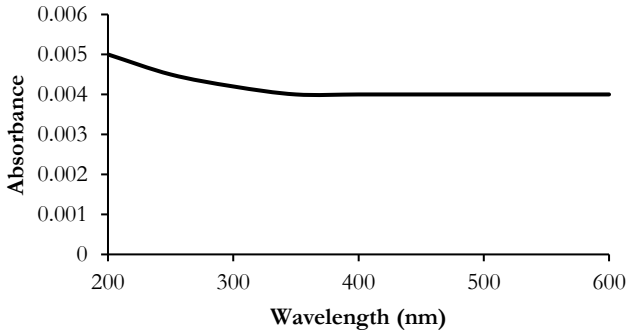

Figure 9. UV spectrophotometer showing no effect of excipients used on optimised emulgel.

CONCLUSIONS

Capsaicin in microemulgel with enhanced therapeutic efficacy was designed, optimized, and developed by improving the topical solubility, permeability, and hence bioavailability of readily available powdered standard capsaicin with extraction. The F8 microemulsion was found to be the best stable optimized microemulsion in terms of RHLB, and 0.6% Carbopol-940 was best for its SI property, which, in turn, stabilized further parameters of 0.05% and 0.1% strength capsaicin emulgels.

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AUTHORS CONTRIBUTION STATEMENT

Ajaya Acharya, Nab Raj Bhatta, Manju Basnet, Ram Sunil Pandey, Nitesh Das, Sujan Karki developed the concept on the research project. All laboratory work was carried out by these researchers. Ajaya Acharya worked on manuscript preparation. Rajan Shrestha, Rajendra Gyawali supervised the work, reviewed the manuscript.

CONFLICT OF INTEREST

The authors do not have any conflict of interest pertinent to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

REFERENCES

Acharya, A., & Bhatta, N.R. (2022). Validation of UV spectrophotometric method for the analysis of capsaicin in ethanol. *International Journal of Pharmacy and Analytical Research*, *11*(2), 115-120.

Ashara, K.C., Paun, J.S., Soniwala, M.M., Chavda, J.R., Mendapara, V.P., & Mori, N.M. (2016a). Microemulgel: an overwhelming approach to improve therapeutic action of drug moiety. *Saudi Pharmaceutical Journal*, *24*(4), 452-457. https://doi.org/10.1016/j.jsps.2014.08.002.

Ashara, K., Soniwala, M., & Shah, K. (2016b). Review article emulgel : A novel drug delivery system. *Journal of Pakistan Association of Dermatologists, 26*(3), 244-249.

Bhattacharya, B., Ghosh, T.K., & Das, N. (2017). Application of bio-surfactants in cosmetics and pharmaceutical industry. *Scholars Academic Journal of Pharmacy, 6*(7), 320-329. https://doi.org/10.21276/sajp

Reyes-Escogido, M.L., Gonzalez-Mondragon, E.G., & Vazquez-Tzompantzi, E. (2011). Chemical and pharmacological aspects of capsaicin. *Molecules, 16*(2), 1253-1270. https://doi.org/10.3390/molecules16021253.

Garg, T., Rath, G., & Goyal, A.K. (2015). Comprehensive review on additives of topical dosage forms for drug delivery. *Drug Delivery, 22*(8), 969-987. https://doi.org/10.3109/10717544.2013.879355.

Godbole, R., Invally, M., Wairkar, S., Bhullar, S., Kaur, G., & Pratapbhai, S. (2018). Formulation, development and evaluation of a novel polymer-based anti-inflammatory emulgel of aceclofenac. *Science International*, 6(2), 71-79.

Jagdale, S., Brahmane, S., & Chabukswar, A. (2020). Optimization of microemulgel for Tizanidine Hydrochloride. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 19*(2), 158-179. https://doi.org/10.2174/1871523018666190308123100.

Khullar, R., Kumar, D., Seth, N., & Saini, S. (2012). Formulation and evaluation of mefenamic acid emulgel for topical delivery. *Saudi Pharmaceutical Journal, 20*(1), 63-67. https://doi.org/10.1016/j.jsps.2011.08.001.

Leppert, W., Malec-Milewska, M., Zajaczkowska, R., & Wordliczek, J. (2018). Transdermal and Topical Drug Administration in the Treatment of Pain. *Molecules, 23*(3), 681. https://doi.org/10.3390/molecules23030681.

Loftsson, T. (2022). Topical drug delivery to the retina: obstacles and routes to success. *Expert Opinion on Drug Delivery, 19*(1), 9-21. https://doi.org/10.1080/17425247.2022.2017878.

Pakhare, A.V, Deshmane, S.V, Deshmane, S.S., & Biyani, K.R. (2017). Design and development of emulgel preparation containing diclofenac potassium. *Asian Journal of Pharmaceutics, 11*(4), S712-S716.

Shah, A.A., Kamdar, K.M., Shah, R., & Keraliya, R.A. (2013). Emulgel: A topical preparation for hydrophobic drugs. *PharmTechMedica*, 2, 370-376.

Shrestha, S., Pokhrel, S., Sharma, S., Manandhar, M., & Alam, I. (2017). Formulation and evaluation of topical microemulgel loaded with terbinafine hcl microemulsion. *International Journal of Pharmaceutical Sciences and Research*, 8(11), 4716-4723.

Torregrosa, A., Ochoa-Andrade, A.T., Parente, M.E., Vidarte, A., Guarinoni, G., & Savio, E. (2020). Development of an emulgel for the treatment of rosacea using quality by design approach. *Drug Development and Industrial Pharmacy, 46*(2), 296-308. https://doi.org/10.1080/03639045.2020.1717515.

Vanti, G., Grifoni, L., Bergonzi, M.C., Antiga, E., Montefusco, F., Caproni, M., & Bilia, A.R. (2021). Development and optimisation of biopharmaceutical properties of a new microemulgel of cannabidiol for locally-acting dermatological delivery. *International Journal of Pharmaceutics*, 607, 121036. https://doi.org/10.1016/j.ijpharm.2021.121036.