RESEARCH ARTICLE

Formulation Development and Evaluation of Microemulsion Loaded Hydrogel Systems with Plant Bioactives in Combination for Treatment of Psoriasis

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ABSTRACT

Psoriasis is an autoimmune, long-lasting skin disorder affecting about 1 to 3% of the world's population. Plant bio-actives like flavonoids, alkaloids, glycosides, terpenoids, phenolic acids, peptides, tannins, etc., are considered as the best alternative over synthetic drugs, especially for the topical treatment of such chronic skin ailments to avoid side effects of such synthetic agents. The present study aims at the formulation and characterization of novel topical carrier systems for the incorporation of plant bioactive molecules from the class of alkaloids and flavonoids so as to enhance the therapeutic efficacy, bypass the side effects of synthetic drugs, and improve drug localization in the diseased skin to achieve site-specific action. This work created oil, surfactant, and co-surfactant formulations of plant bio-actives using oleic acid, polysorbate 80, and propylene glycol. Different batches of microemulsions with surfactant: Cosurfactant composition ranging from 25 to 34.8% were prepared and were embedded in a hydrogel system containing gelling agents like sodium alginate and carbapol 940 to get ease of topical application in the treatment of psoriasis. These developed micro-emulates (microemulsion loaded hydrogels) were evaluated for various parameters like viscosity, spreadability, content uniformity, microscopic examination, globule size, zeta potential, polydispersibility index, centrifugation test, dilution test, dye test, percent transmittance, conductivity test, etc. The developed formulations were pharmaceutically stable and efficient.

Keywords: Bio-actives, Hydrogel, Microemulgel, Microemulsion, Psoriasis.

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INTRODUCTION

Skin is the body's protective layer, which plays an important role in protecting the body from various types of shocks, radiations, toxic substances and different environmental insults.[1] A total of 1 to 3% of people worldwide suffer from psoriasis, a psychosocially and occasionally medically disabling autoimmune inflammatory illness that is characterized by thicker, erythematous, and scaling plaques that frequently flare up and then fade away.[2,3] It may affect any part of the body. However, the commonest site are the sacrum, scalp, and extensor surfaces of the elbows and knees. Hands and feet are commonly involved. Psoriasis is not characteristically itchy but may be very inflamed, rapidly spreading, or involving the palms and sole.[4]

Many plants and their isolated active ingredients have been used in traditional psoriasis medicinal systems; they could serve as safer substitutes for the traditional course of treatment.[5] Some plant bio-actives possessing well-known antioxidant, anti-inflammatory or anti-psoriatic potential could be used to find new opportunities in topical treatment of psoriasis, like berberine,[6,7] quercetin,[8,9] etc. These can be used in various combinations for the treatment of psoriasis. These plant bio-actives are associated with many limitations, including low solubility and bioavailability.

Novel drug delivery systems have several advantages over conventional ones, including enhanced bioavailability, therapeutic activity, strength, tissue distribution, prolonged delivery, physical and chemical degradation resistance, and higher solubility.[10,11] Micro-emulsions are clear dispersion of 2 immiscible solutions, for instance, oil and water, which are thermodynamically stable, with very low interfacial tension and range of size 10 to 200 nm, stabilized by means of the

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interfacial film of surfactant and cosurfactant molecules, due to their special solubilization qualities. Microemulsions have garnered significant interest as possible drug delivery methods, either as topical administration systems or as ways to improve the bioavailability of active pharmacological compounds that are poorly soluble in water.

Although microemulsions are advantageous in many ways, their stability may alter due to low viscosities. To overcome this inadequacy, ME can be successfully embedded into crosslinked hydrogel systems to achieve microemulgels with higher viscosity and, hence, better stabilized.[12]

MATERIALS AND METHODS

Materials

Berberine chloride and quercetin were procured from Ottochemie Pvt. Limited, Mumbai for said work. All remaining chemicals of were procured from Loba Chemie Pvt. Ltd, Mumbai, India.

Methods

Fourier-transform infrared

The BER, QCT, and FA samples were analyzed using the KBr pellet technique, and the resulting spectra were recorded by an fourier-transform infrared (FTIR) spectrophotometer (FTIR-8400S Shimadzu Crop, Japan) (Figures 1 and 2). We used a hydraulic press to gently mix each ingredient with KBr in a 1:1 ratio to make the pellets. To learn the pellet's characteristic spectra, we recorded its spectra between 4000 and 400 cm^{-1} and compared them to the analysis's standard reference. Every single medicine, every possible combination, and every drug-excipient combination had its spectra recorded.

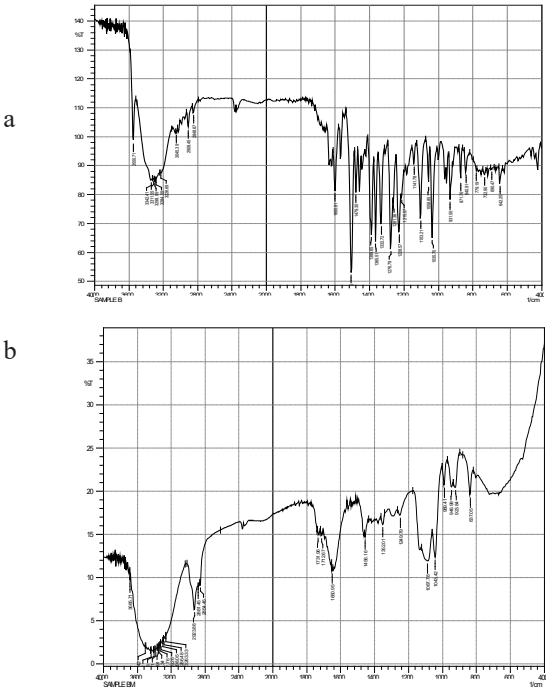

Figure 1: FTIR spectra of (a) Pure berberine, (b) Berberine-excipient mixture

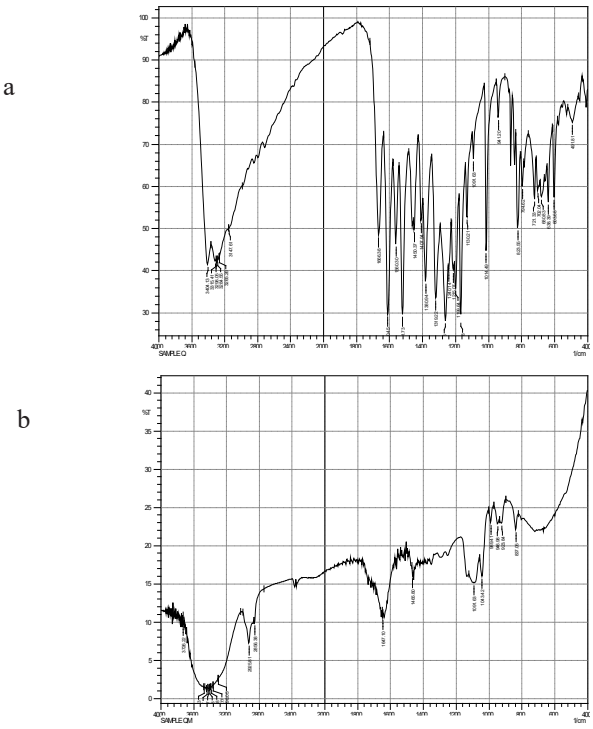

Figure 2: FTIR spectra of (a) Pure quercetin (b) Quercetin - excipient mixture

Assortment of oil, surfactant and co-surfactants based on solubility

One useful step in screening oil surfactants and co-surfactants affording to maximal solubility was doing a solubility of pharmaceuticals in different oils, surfactants, and co-surfactants. The following ingredients were utilized for the solubility test: Surfactants (Tween 20, Tween 60, and Tween 80), oils (isopropyl myristate, oleic acid, and olive oil), and co-surfactants (ethanol, isopropyl alcohol, propylene glycol, and PEG 400). Separately, excess amounts of BER and QCT were added to test tubes containing solvents (Oil/Surfactant/Cosurfactant) and then vortexed for 72 hours at room temperature. Centrifuging solution at 3000 rpm for 10 minutes after 72 hours eliminated any medication that had not dissolved. About 10 µL of the supernatant was transferred to a microcentrifuge tube, and 1-mL of methanol was added to get volume up to 1-mL. A 0.22-µm nylon filter was used to filter the produced liquid after it had been vortexed. We next tested the absorbance for BER at 366 nm. The unknown concentration of BER and QCT dissolved in the oils were measured by utilizing previously plotted UV standard calibration curves of the respective medications. After appropriate dilution, the absorbance of QCT was recorded at 348 nm.

Screening of surfactant and co-surfactant ratio for microemulsion

It was the ME region that dictated the surfactant-to-co-surfactant ratio. Water titration wasutilised to create pseudo ternary phase diagrams for oil, water, surfactant, and cosurfactant. Recognition to this, we were able to identify the

ingredients and the concentration ranges that may produce a microemulsion with a big potential existence area on the ternary plot. As previously calculated, vortexing was used to mix the surfactant and cosurfactant in mass ratios of 1:1, 2:1, and 3:1. Following this, oil was mixed with portions of every surfactant and cosurfactant mixture (S_{mix}) while the mixture was at room temperature. For every phase diagram, oil-to-Smix ratio varied, going from 9:1 to 8:2 to 7:3 to 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9 (equivalent weight to water). A magnetic stirrer was used to vigorously stir each mixture when water was added one by one.

The point at which the solution turned turbid was recorded as endpoint and was plotted on the ternary plot to construct a phase diagram. The microemulsion zone of existence was defined as the space these points occupied. All three phases' quantities were recorded in %w/w.[13]

Method of preparation of bioactive loaded microemulsion

By dissolving 0.5% (w/w) bioactives in 0.6% (w/w) oleic acid, bioactive loaded O/W ME was created. The oil phase was mixed with various S_{mix} ratios of Tween 80 and PG using a vortex mixer and ultra sonicator. The above mixture and double distilled water were then heated on a water bath separately upto 60 to 70°C. Then the DDW was slowly added drop-wise with the help of a syringe with continuous stirring on a high-speed homogenizer at 3500 rpm for 40 minutes till clear microemulsion was obtained. The microemulsions containing berberine and quercetin were prepared in a distinct way. Another formulation was prepared using a combination of both berberine and quercetinin.

Method of preparation of microemulsion loaded hydrogel

To make the hydrogel base, we soaked sodium alginate and carbapol 940, two gelling agents, in DDW for 24 hours in the amounts specified. Optimized ME was added slowly to the prepared hydrogel base, stirring on a high-speed homogenizer at 1200 rpm to get ME-loaded hydrogels.

Characterization and Evaluation of Optimized microemulsion

Viscosity

Brookfield viscometer was used to measure viscosity. The microemulsion's viscosity was determined by immersing spindle number 2 in it and spinning it at 50 rpm at room temperature. Using a particular depth of immersion and rotation at room temperature, the viscosity of hydrogel and microemulsion loaded hydrogel was resolute through spinning spindle number 6 at a speed of 50 rpm.

pH determination

The formulations' pH levels were measured using a digital Systronic pH meter. The hydrogel, which was filled with microemulsions, was dissolved in distilled water to produce a tenfold diluted solution. The pH meter was calibrated before to each utilizing buffer solutions (pH 4.0, 7.0, and 9.2). Three separate pH measurements were made, and means were computed.

Dilution test

The prepared ME was diluted with DDW in ratios like 1:10 and 1:100, and resulting dilutions were checked for any signs of separation.

Dye solubility test

Methyl orange, a water-soluble dye, was introduced to formulate ME system, and the dye's solubility was used to assess the phase system of ME.

Percent transmittance

The prepared ME formulations were diluted with DDW and checked for percent transmittance using UV-visible Spectrophotometer at 630 nm.

Conductivity test

The prepared ME was diluted 10 to 100 times with DDW, and the resulting dispersion's conductivity was recorded using a Systronic conductivity meter.

Refractive index determination

Refractive index measurements for all tested microemulsions were done using Abbe's Refractometer. The refractive index was recorded following the normal method after placing the undiluted ME sample directly on the cleaned surface of the lower prism of the refractometer.

Globule size, Zeta potential and PDI

Optimized ME was assessed for, size distribution profile, globule size and zeta potential and poly-dispersibility index was recorded over Horiba SZ 100.

Extrudability test

A simple approach was used to assess extrudability: weight in grams mandatory to extrude a 0.5 cm gel ribbon from a collapsible tube in 10 seconds was determined.

Crimped end of a closed, collapsible tube filled with gel was firmly pushed. After removing the cap, the gel was let to extrude until the pressure subsided. Extrudability improves with increased extrusion quantity. Next, the extrudability is evaluated using formula:

$$\text{Extrudability} = \text{Applied weight to extrude gel from tube (in gm)/Area (in cm}^2\text{)}$$

Extrudability of gel was tested three times, with mean value being reported.

Centrifugation test and thermodynamic stability testing

All the developed formulations were centrifuged at 3500 rpm in REMI cooling centrifuge C-24 and checked for phase separation. Phase-separation-free formulations were used for freeze-thaw and heating and cooling cycles. Between 4 and 45°C, six cycles were run by storage at both temperatures for at least 48 hours.

For additional research, the formulations that remained stable at these temperatures were chosen.[14] The thermodynamic stability was determined based on parameters like phase separation, drug precipitation and clarity.

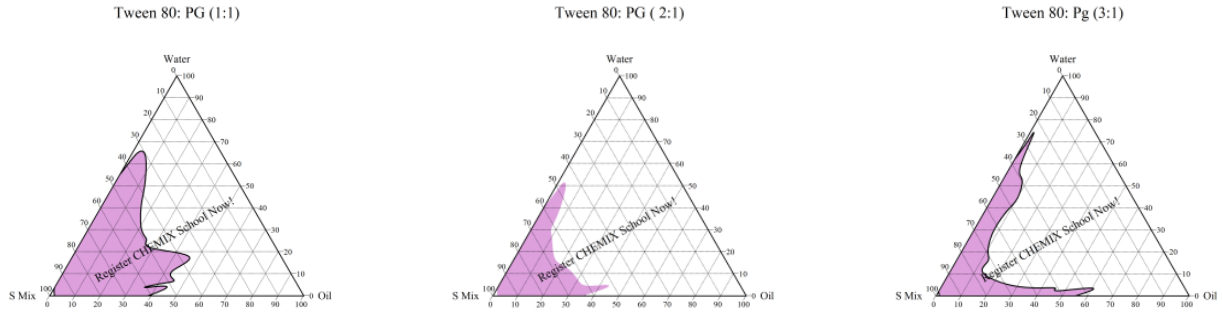

Figure 3: Pseudo ternary phase diagrams for selection of suitable S:CoS ratio for preparation of microemulsion

Stability studies

The hydrogel with optimized ME loading was placed inside lacquered aluminum collapsible tubes and kept for a duration of six months at 3 distinct temperatures: 5 ± 3°C, 25 ± 2°C, and 40 ± 2°C. After predetermined times, samples were taken out and assessed for color change, globule size, PDI, viscosity, pH, percent transmittance, clarity, and non-grittiness.

Ex-vivo drug permeation studies

As described in literature, vertical Franz diffusion cell assembly was used to complete the research using goat skin that had been removed after making a few adjustments.[15] With the stratum corneum exposed to the donor compartment, the excisional skin was sandwiched between the Franz diffusion cell's donor and receiver compartments. Next, a predetermined amount of micro-emulgel was administered to the donor compartment's skin. As the receptor media, phosphate buffer saline (PBS) with a 6.4 pH was utilised. The cell contents were kept at 37 ± 1°C and constantly swirled at 100 rpm using a magnetic stirrer. Periodically, a 1-mL aliquot was removed from the receptor chamber's sampling arm at appropriate intervals and replaced with an equivalent volume of brand-new buffer. Filtering all of the gathered samples using Whatmann filter paper allowed us to estimate the cumulative %of drug release.

RESULTS AND DISCUSSIONS

Testing solubility of surfactants, oilsand co-surfactants for screening purposes: Research on solubility of pharmaceuticals in different oils, surfactants, and co-surfactants: Having medications that dissolve well in different parts of the ME system is crucial for developing a stable ME. The three medications were found to be most soluble in a combination of oleic acid, tween 80, and propylene glycol, an oil, surfactant, and co-surfactant.

Screening of surfactants and co-surfactant ratio for microemulsion: Pseudo ternary phase diagrams for surfactant: cosurfactant ratio of 1:1, 1:2, 1:3 was constructed and maximum micro-emulsion region was observed with the ratio of 1: 1 so it was selected for further formulation development (Figure 3).

Microemulsions filled with bioactive substances and microemulgels thickened with hydrogel: By combining 0.5% w/w drug combinations with 6.6 to 6.8% oil, O/W microemulsions of varying concentrations were created. The 25 to 35% surfactant cosurfactant ratios were tried, and the 31 to 33.6% batches were optimized based on various parameters. The prepared microemulsions were added to previously swollen hydrogel bases under high shear (Tables 1 and 2).

Table 1: Composition of blank hydrogel batches

Hydrogel base	*Carbapol 940 (%w/w)*	*Sodium alginate (%w/w)*	*Water (%w/w)*	*Consistency*
G1	1	0	99	Fluid gel
G2	2	0	98	Fluid gel
G3	1	2	97	semi fluid gel
G4	1	3	96	Semi stiff gel
G5	2.5	2.5	95	Stiff gel

Characterization and Evaluation of Optimized Microemulsions

Viscosity

Optimized microemulsions were found to have viscosity of 75 to 125 cps. The viscosity of hydrogels containing sodium alginate and carbapol 940 in different ratios was determined. Among them, the gel base with viscosity of 1532 cP was selected for incorporation of drug-loaded micoemulsion.

pH determination

The pH was determined for all the optimized batches and it was found to be between 6.4 to 7.1 which was within the limit for topical formulations.

Percent transmittance

The developed microemulsions were tested for percent transmittance on UV-visible spectrophotometer and all batches were found niform, clear, free of precipitates, optically isotropic, and yellow in hue.

Refractive index test

An Abbe's refractor measured the microemulsion's refractive index at 25 ± 0.5°C. The mean refractive indices for the blank formulation were found tobe in the range from 1.365 to 1.3835 as listed in Table 3.

Dilution test

To examine for evidence of separation, the produced microemulsions were diluted with double distilled water at ratios of 1:10 and 1:100. The optimised microemulsion

Table 2: Composition of optimized formulation batches of microemulsions and microemulsion loaded hydrogels

Formulation → Content (%w/w)↓	*ME1*	*ME2*	*ME3*	*ME4*	*BMG*	*QMG*	*BQMG*
Berberine	-	-	-	-	0.5	-	0.25
Quercetin	-	-	-	-	-	0.5	0.25
Oil	6	6	6.6	7	6	6.6	7
S_{mix}	31	33.32	33.6	32.5	33.32	33.6	32.5
Carbapol 940	1	1	1	1	1	1	1
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Sodium alginate	3	3	3	3	3	3	3
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Triethanolamine	2	2	2	2	2	2	2
Double distilled water (DDW)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 3: Viscosity, percent transmittance, refractive index and ph of blank microemulsion batches

Formulation	*Viscosity (cP)*	*Percent transmittance*	*Refractive index*	*PH*
ME1	75.45	94.3	1.3715	6.5±0.2
ME2	90.02	95.11	1.3715	6.6±0.2
ME3	121.57	93.8	1.3835	6.7±0.2
ME4	124.32	94.5	1.378	6.4±0.2

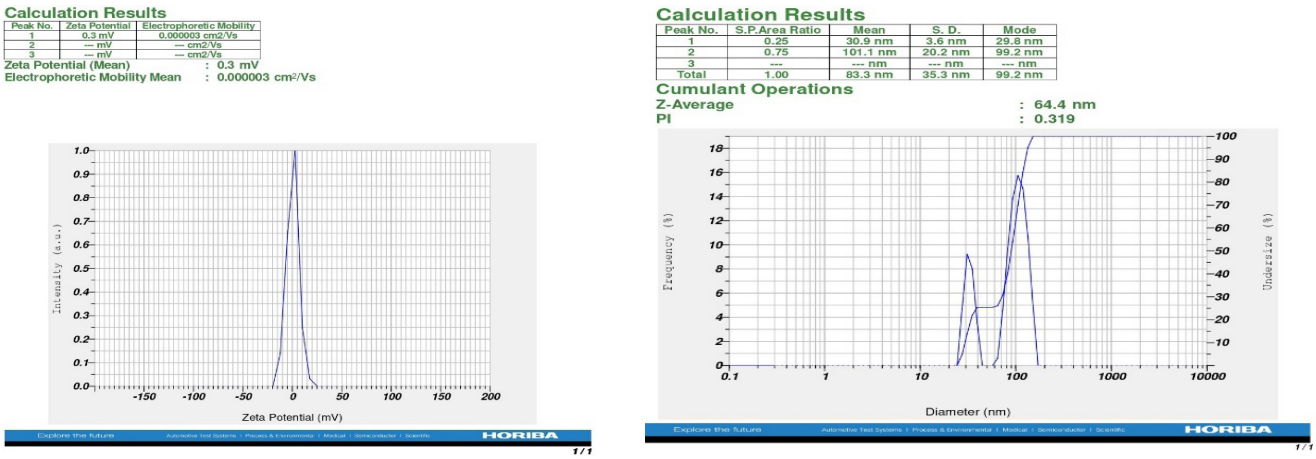

Figure 4: Zeta potential, PDI and globule size of optimized microemulsion batch

exhibited no phase separation symptoms. It confirmed that the water is present as continuous phase.

Dye solubility test

The results of the dye solubility test demonstrated that methyl orange, a water-soluble dye, distributed evenly during the ME system, indicating that produced ME was of the o/w type.

Globule size, zeta Potential, PDI and conductivity

globule size, zeta potential PDI and conductivity test for developed formulations were performed as per standard procedures and results obtained were in acceptable range. The results of above tests are compiled in Figure 4 and Figure 5.

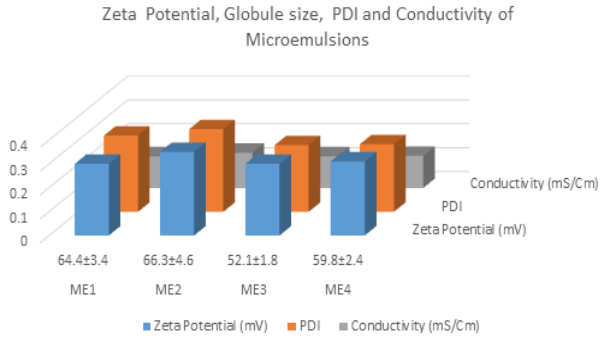

Figure 5: Globule size, polydispersibility index, zeta potential, and conductivity of optimized microemulsion batches

Table 4: Centrifugation and thermodynamic stability of drug-loaded microemulsion-embedded hydrogels

Formulation	*Phase separation, drug precipitation and clarity*			*Inference*
	Heating cooling cycle	*Freez thaw*	*Centrifugation*	
BM1	√	X	X	Fail
BM2	√	√	√	Pass
BM3	√	√	X	Pass
BM4	X	√	√	Pass
QM1	√	√	X	Pass
QM2	X	X	√	Fail
QM3	√	√	√	Pass
QM4	√	√	X	Pass
BQ1	√	X	√	Pass
BQ2	√	X	√	Pass
BQ3	X	√	X	Fail
BQ4	√	√	√	Pass

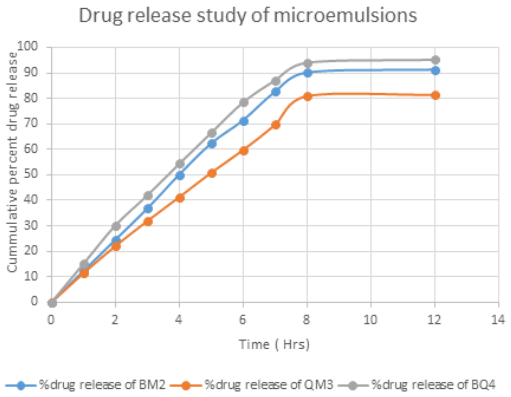

Figure 7: Release studies of microemulsion loaded hydrogels

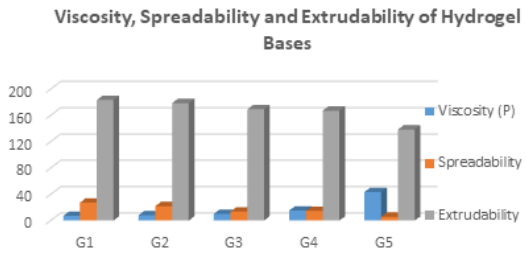

Figure 6: Viscosity, spreadability and extrudability of developed microemulsion-embedded hydrogels

Spreadability test

Spreadability results of developed in-house hydrogels were found to be in the range of 5.84 to 27.37 gcm/sec as shown in the table. Figure 6 illustrates the improved microemulsion-based hydrogel's spreadability, which was determined to be 14.62 gcm/sec.

Extrudability test

Extrudability is useful to determine ease of dose delivery from the collapsible tube. It was determined in triplicate, and the results obtained were 138.46 to 183.26 gm/cm^2.

Centrifugation, thermodynamic stability and stability study of developed microemulsion embedded hydrogels

The results obtained for centrifugation, thermodynamic stability and stability studies were found satisfactory and are mentioned in Tables 4 and 5, respectively.

Research on drug content, viscosity, percent transmittance, and refractive index: Drug's loaded viscosity, transmittance percentage, and refractive index following the steps allowed us to identify hydrogels containing microemulsions. We diluted it with the right solvent and used HPLC to analyze the results to find out how much medicine was in optimized microemulsion-embedded hydrogel.

Table 5: Viscosity, percent transmittance, refractive index and drug content of drug loaded microemulsion embedded hydrogels

S. No.	*Formulation*	*Viscosity (cP)*	*Percent transmittance*	*Refractive index*	*Drug content*
1	BM2	92.34	94.86	1.4216	97.08%w/w
2	QM3	120.82	93.1	1.4246	98.49%w/w
3	BQ4	125.08	93.8	1.4203	98.09%w/w

Table 6: Stability study of the optimized ME formulations

T°C RH %	*Time (Days)*	*Globule size*	*PDI*	*pH*	*Viscosity (cP)*	*RI*	*%T*
4°C ± 2°C 60% ± 5%RH	30	66.3 ± 4.6	0.279	6.7 ± 0.1	92.32 ± 1.89	1.4125	95.11
	60	66.8 ± 2.9	0.291	6.8 ± 0.4	92.45 ± 1.64	1.4026	95.1
	90	67.9 ± 3.1	0.283	6.8 ± 0.3	92.56 ± 1.79	1.4211	94.85
25°C ± 2°C 60% ± 5%RH	30	67.7 ± 1.8	0.293	6.6 ± 0.3	91.47 ± 1.62	1.4255	94.3
	60	68.2 ± 3.6	0.307	6.7 ± 0.2	91.53 ± 1.48	1.4265	94.21
	90	71.4 ± 2.8	0.319	6.8 ± 0.1	91.56 ± 1.94	1.4309	91.03
40°C ± 2°C 75% ± 5%RH	30	68.3 ± 2.4	0.332	6.5 ± 0.2	91.56 ± 1.34	1.4195	94.5
	60	72.6.9 ± 3.2	0.358	6.4 ± 0.3	90.02 ± 1.32	1.4207	94.12
	90	74.3 ± 3.6	0.402	6.5 ± 0.2	90.26 ± 1.45	1.4234	93.21

Ex-vivo drug release studies

Ex-vivo drug release studies were achieved in phosphate buffer saline (pH 6.4). All developed formulations were found to give good drug release of 12 hours. The outcomes are compiled in Figure 7. Stability studies are mentioned in Table 6.

CONCLUSION

The study found that berberin and quercetin skin permeability and solubility can be increased by using microemulsion. Sodium alginate and carbapol 940 were used to successfully construct a microemulsion-based hydrogel. The gelling agent added viscosity to the preparation and prolonged the drug's activity by lengthening its residence time at the application site. The berberine and quercetin (0.5%), oleic acid (6–7%), tween 80, propylene glycol (31–33.6%, 1:1), water (54-64%), sodium alginate, and carbapol 940 (4%), were the constituents of the final created microemulsion embedded hydrogel. The hydrogel that was developed with microemulsion embedded in it was optimized in terms of viscosity, medication content, and skin irritancy. Even after six months of stability, the microemulsion's globule size, pH, viscosity, refractive index, and PDI did not alter. Thus, the prepared microemulsion has shown good stability at different temperatures like 4, 25 and 40℃ and 60 to 75% relative humidity for 6 months.

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