https://doi.org/10.48047/AFJBS.6.12.2024.4667-4681

Formulation and Optimization of Fluticasone Propionate loaded microemulsion for Enhanced Topical Applications

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Article History
Volume 6, Issue 12, 2024
Received: June 10, 2024
Accepted: July 5, 2024
doi:
10.48047/AFJBS.6.12.2024.4667-4681

Abstract
This study investigates the optical characteristics and calibration information Fluticasone propionate in various solvents, focusing specifically on methanol and phosphate buffer (PBS) with the addition of Tween 80. Concentrations ranging from 5 to 40 µg/ml were used to produce calibration curves. The average absorbance, together with the corresponding standard deviations, in the methanol calibration data exhibited properties of linearity and repeatability. In addition, the high regression coefficient (R^2) of 0.999 provides additional evidence of the great conformity to Beer-Lambert's rule. The PBS-Tween 80 solution had a high degree of linearity, as shown by its R^2 value of 0.999, confirming its consistency when tested with different solvents. In addition, the pre-formulation research of Fluticasone propionate (FP) provided insights into its physicochemical properties and its compatibility with various excipients, showing no significant interactions under normal conditions. Through the use of pseudo-ternary phase diagrams and experimental methodologies, the study aims to improve the solubility and stability of the components in order to develop a microemulsion formulation for FP. The solubility and globule size of the optimised formulation were both at their optimum levels, resulting in a considerable enhancement in the potential of FP for topical application. The results highlight the reliability of the analytical methods used to calibrate Fluticasone propionate and the effective formulation approach utilised for FP Microemulsions. These findings provide valuable insights for prospective pharmaceutical applications in the future.
Keyword: Fluticasone propionate, Tween 80, Tween 20, Campul MCM, Oleic acid, Microemulsion

1. Introduction:

The prevalence of skin problems and diseases is rapidly increasing, affecting a significant number of people on a daily basis. Skin illnesses are mostly caused by a variety of infectious pathogens or inflammatory conditions, both of which provide significant challenges [1]. Various skin-related disorders, such as vitiligo, psoriasis, atopic dermatitis, and carcinomas, include a wide range of illnesses that may range in severity from harmless to potentially life-

threatening. Scientific research indicates that dermatological illnesses are very severe and regularly impact the populations of many developing countries. Despite notable progress in dermatological treatments, there are certain skin-related problems that are difficult to control, especially those linked to infectious skin illnesses. Psoriasis, atopic dermatitis, and allergic contact dermatitis are chronic skin illnesses characterised by the presence of inflammatory T cells and increased release of cytokines in the afflicted regions [1].

Microemulsions are distinguished by their transparency and thermodynamic stability, which may be ascribed to the accurate ratios of surfactant and water within their particle size range of 10 to 100 nm [3]. The constituents of the microemulsion may accelerate the pace at which drugs pass through the stratum corneum by reducing the diffusion barrier [4].

2. Material and Methods

2.1Preparation of Calibration curve in menthol: A 25 ml volumetric flask was filled with 25 milligrams of Fluticasone propionate after precise measurement. One 1 mg/ml methanol solution was used to modify the volume to the required level, and a tiny amount of methanol was added to guarantee full dissolution of Fluticasone propionate. Using a pipette, precisely 5 mL of the solution mentioned before was transferred to a 50 mL volumetric flask. The stock solution had a concentration of 100 µg/ml when a certain quantity of methanol was added [5].

2.2 Determination of $\lambda_{max:}$ In order to get the appropriate volume in a 10 ml volumetric flask, 1 ml of the stock solution was diluted with methanol. The Fluticasone propionate solution (10 µg /ml) is scanned into the wavelength range of 200nm to 400 nm by methanol as a reference [6].

2.3 Preparation of calibration curve:: Using a pipette, specific volumes of 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 ml were accurately taken from the original solution and transferred to individual 10ml volumetric flasks. Methanol was added to reach the desired volume, resulting in final concentrations of 10, 15, 20, 25, 30, 35, 40, and 45 µg/ml. The absorbance of each of the produced solutions was measured at the absorption maxima, using methanol as the baseline. Every measurement was recorded three times [7].

2.4 Preparation curve of PF in phosphate buffer pH 6.8:

2.4.1 Preparation of stock solution: After accurate measurement, 25 milligrams of Fluticasone propionate was placed into a 25 ml volumetric flask. A little amount (1-2 ml) of methanol was added to completely dissolve Fluticasone propionate. Afterwards, a solution of PBS 6.8 at a concentration of 1 mg/ml tween 80 was added to reach the desired volume. A carefully measured volume of 5 ml was extracted from the solution in issue using a pipette and then moved to a 50 ml volumetric bottle [8].

2.4.2 Preparation of calibration curve: Aliquots of 1, 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 ml were withdrawn from the stock solution using a precision pipette. Subsequently, these portions were transferred to individual 10 ml volumetric flasks, and the volume was modified to the required level using PBS 6.8 solution containing 1% excipient. The ultimate concentrations obtained from this technique were 10, 15, 20, 25, 30, 35, 40, and 45 µg/ml. The measurements were recorded three times [9].

2.5 **FTIR spectra of drug:**A FTIR spectrophotometer manufactured by Shimadzu Corp. of Japan was used to identify the medications. A 100 mg dose of KBr powder was combined with a 1-2 mg sample. For two or three minutes, the ingredients were crushed using a pestle and mortar. We measured the mixture's infrared spectra between 4000 cm-1 and 400 cm-1 after placing it in a sample container [10].

2.6 Drug and Excipients compatibility examination: The 10 mg medications were dissolved in 5 ml of selected oil, surfactant, and co-surfactant in vials, and then stored at room temperature

(25°C) for one month. The petri dishes contained a mixture of Fluticasone propionate and Carbopol 934P. Weekly, the concentration and discoloration of the pharmaceutical mixtures and solutions were evaluated [11].

2.7Development of pseudo-ternary phase diagrams: The concentration range of the microemulsion components was determined by creating pseudo-ternary phase diagrams using aqueous titration. A range of 3:1, 2:1, 1:1, and 1:2 were used to adjust the surfactant-to-co-surfactant ratio (Smix). We produced thick mixes of surfactant, oil, and co-surfactant in order to construct pseudo-ternary phase diagrams with accurate Smix ratios. There was a 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 oil-to-Smix volume ratio. Using a magnetic stirrer at room temperature, the oil and Smix mixture was progressively diluted with double-distilled water using the water titration procedure. Each drop was added while swirling. A microemulsion that was both transparent and clear was considered to be the end result of the aqueous titration process. To generate the pseudo-ternary phase diagram, the component concentrations were subsequently determined [12].

2.7.1Preparation of Fluticasone propionate loaded microemulsion: Based on the pseudo ternary phase diagrams, we selected the Smix ratio that resulted in the biggest oil-in-water microemulsion area. The design points in the D-optimal design space dictated the oil and Smix ratios that were used. A solution of Fluticasone propionate and an oil/Smix combination was prepared at room temperature and stirred with a magnetic stirrer. A microemulsion, which is transparent and easy to see through, is created by slowly adding measured amounts of distilled water to an oily combination. After 15–20 minutes of gentle whirling with a magnetic stirrer, the mixture should have stabilised and reached equilibrium. It was then left at room temperature together with all the otherMicroemulsions, including FP.

2.8Physicochemical characterization ofMicroemulsions loaded with FP:

2.8.1 Organoleptic parameters: The organoleptic characteristics were assessed using a visual examination of the prepared microemulsion.

2.8.2 Microscopy of transmission electron: The formulation's microstructure was examined using the TEM method. A copper film grid covered with holey carbon was immediately applied with a diluted sample. She then added a 1% phosphotungstic acid solution to the mixture. After removing any excess phosphotungstic acid, the sample was dried and processed with filter paper [13].

An electron transmission microscope (TEM; CM12 Philips, USA) was used to analyse the formulations' dimensions and morphology.

2.8.3 Zeta potential and drop size distribution: A mixture of 1 ml of microemulsion and 10 ml of distilled water was prepared at a temperature of 37 ± 0.5˚C. The zeta potential and distribution of droplet sizes were measured after the emulsions were prepared by gently swirling them with a magnetic stirrer for 10 minutes. As a method for estimating droplet size, laser diffraction (Malvern Instruments, Malvern, UK) was administered [14].

2.8.4 Polydispersity Index: The procedure remains unaltered from the one used to ascertain particle size.

To determine the range of particle sizes in a certain system, the degree of polydispersity is measured [15]**.**

$$\frac{\textit{No. of particles having size grater than 100nm}}{\textit{No. of particles having size less than 100nm}}$$

Regarding the polydispersity index (PDI), it is mentioned.

2.8.5pH: At a temperature of 25 ±1 ℃, a systronic digital pH meter was used to test the microemulsion pH. Each formulation pH was measured three times before usage, and the pH meter was calibrated beforehand [16].

2.8.6 Viscosity Determination: The viscosity was determined using the Brookfield viscometer DVII plus pro, a rotational device for measuring viscosity manufactured by the Brookfield engineering laboratory in the United States. The viscosity was measured at a temperature of 300 degrees Celsius and a rotational speed of 60 revolutions per minute using the LV1 spindle. The measurement was repeated one minute after the rotation of the spindle. The research used fresh samples to do the experiment three times, and the results were presented as the average value plus or minus the standard deviation [17].

2.8.7Dilution test: The emulsion's capacity to mix evenly with the liquid that makes up its continuous phase is the basic premise of dilution testing. Diluting the system is an integral part of the microemulsion process, regardless of whether an oil or water phase is employed. Therefore, the microemulsion may be watered down in an oil-in-water (o/w) system. The opposite is true for water-in-oil (w/o) microemulsion, where the oil is used to dilute the system.

2.8.8Scattered reflection Fourier Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFTS): Soft Introspection The medicine and drug-excipients were physically mixed and subjected to Infrared Fourier Transform Spectroscopy (DRIFTS) on a Shimadzu Corp., Japan, and FTIR 8400S instrument to increase the likelihood of finding such interactions. The medication was analysed using Fourier transform infrared spectroscopy (FTIR) to determine its physical composition in the presence of isopropyl myristate, Cremophor EL, and isopropyl alcohol. Utilizing the DRIFTS technique, 1-2 ml of the material was mixed with 100 mg of KBr Powder. For two or three minutes, the mixture was pounded with a pestle and motor. Infrared spectra were taken of the mixture in the 400–4000 cm–1 range using a sample container. It is considered an interaction when the drug standard peak is absent from the FTIR spectra of mixes that include excipients [18].

2.8.12 Stability study:

For six months, the ICH-required stability experiments of ME were conducted in amber-colored glass containers under three distinct storage conditions: 2-8 °C, 25±2 °C/60% RH±5% RH, and 40±2 °C/75% RH±5% RH. All of the storage areas were securely sealed. Samples were removed at six-month, three-month, and zero-month intervals, as specified. The samples underwent the following tests while they were in storage [19]:

3. Results and discussion

3.1 Examination of calibration of curve

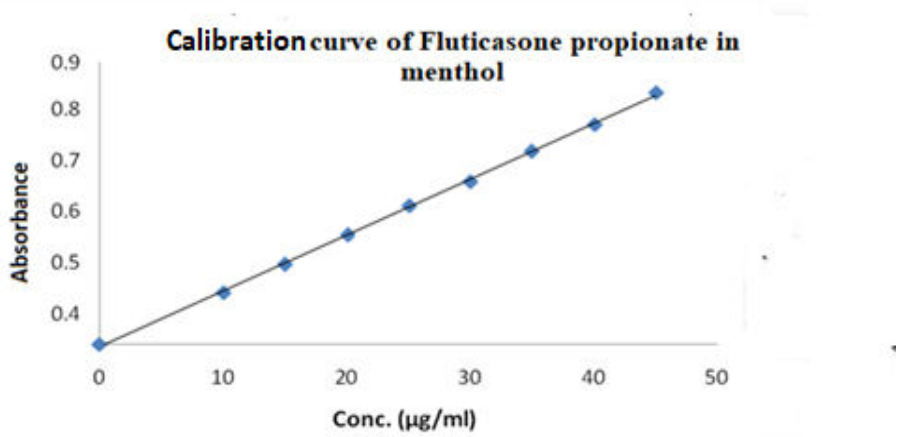

Figure1: CalibrationcurveofPFinmethanolat255nm

3.2Calibration curve of PF in phosphate buffer pH 6.8:

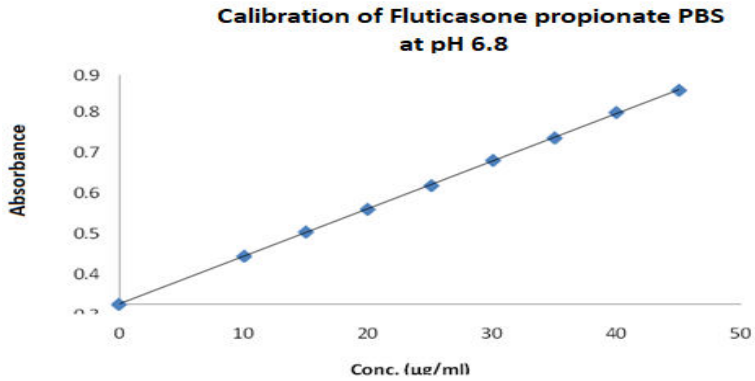

Figure2:CalibrationcurveofPFinPBSpH6.8containing1% Tween 80 at 255 nm

3.3 FTIR Spectrum of Fluticasone propionate

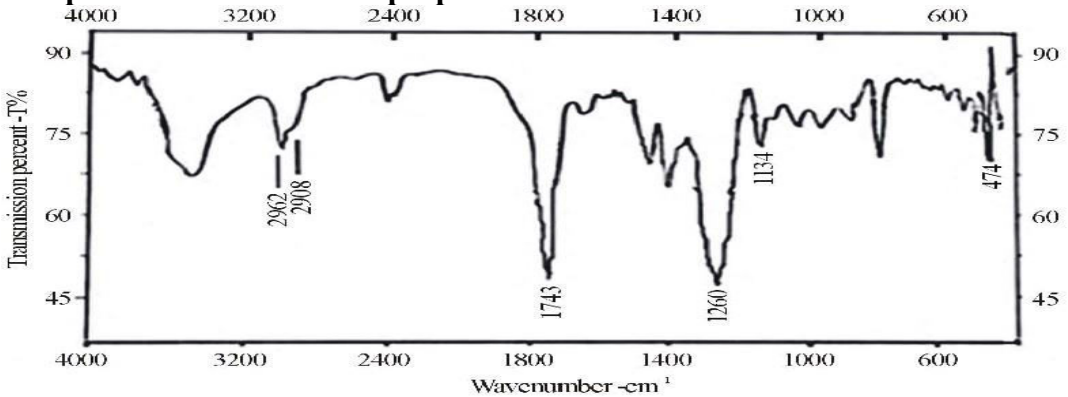

Figure3: FTIR spectra of Fluticasone propionate

3.4 Examination of drug and excipient compatibility study:

Research like this involves simulating the normal circumstances for making, keeping, and giving the medication, as well as testing the stability of a potential drug candidate when exposed to various excipients. Results showed that under different conditions, the medicine does not react negatively with the listed excipients [20].

Table 1: Examination of drug and excipient compatibility study

Time in weeks	Parameters	FP:IPM	FP:Cremophore EL	FP:IPA
0	Transparency	Transparent	Transparent	Transparent
	Drug content	99.97±0.88	99.86±0.73	99.59±0.34
1	Transparency	Transparent	Transparent	Transparent
	Drug content	99.67±0.67	99.72±0.44	99.32±0.24
2	Transparency	Transparent	Transparent	Transparent
	Drug content	99.03±0.98	99.23±0.45	98.90±0.44
3	Transparency	Transparent	Transparent	Transparent
	Drug content	99.02±0.43	99.19±0.76	98.78±0.98
4	Transparency	Transparent	Transparent	Transparent
	Drug content	98.92±0.65	98.99±0.78	98.88±0.79

3.5Formulation and characterization of microemulsion of FP:

3.5.1 Assessment of constituents for microemulsion formulation: To choose the most suitable oils, surfactants, and co-surfactants for the microemulsion, the solubility of FP was tested in a range of solutions. Table 2 shows that their improved solubility had a role in their selection.

Table 2: The solubility of FP in different oils, surfactants as well as co-surfactants.

Sr. No.	Component	Solubility in mg/ml
Oils		
1	Isopropyl Myristate (IPM)	58.06±0.98
2	Campul MCM	29.88±2.1
3	Oleic acid	32.09±0.66
4	Captex 355	18.30±2.8
5	Captex 200	16.87±2.98
Surfactant		
6	Tween 20	40.08±2.34
7	Tween 60	50.34±1.67
8	Tween 80	43.09±0.44
9	Cremophore EL	52.06±2.35
10	Labrasol	45.89±1.67
11	Cremophore RH 40	44.08±0.33
Cosurfactants		
12	PGE 600	17.89±0.98
13	PEG 400	19.55±0.99
14	Transcutol P	32.44±1.43
15	Iso-butyl alcohol (IBA)	54.09±1.27
16	Glycerol	24.90±0.9
17	Iso-propyl alcohol (IPA)	59.45±0.67

3.5.2 Compatibility Examination: Various ratios of surfactant to cosurfactant (Smix) and oil to Smix were tested for compatibility. Only five milliliters remained of the whole concoction. The findings from the research examining compatibility are shown in Table 3.

Table 3: Compatibility investigations were conducted on a specific combination of oil, surfactant, and co-surfactant for FP microemulsion.

Ratio differentiation	Examination			
	Cemophoren LE:IPA (Smix)		IMP:Smix	
1:4	12 hr	24 hr	12 hr	24 hr
1:3	0	1	0	0
1:2	0	0	0	0
1:1	0	0	0	0
2:1	0	0	0	0
3:1	0	0	0	0
4:1	1	1	0	1

3.5.3 Development of pseudo-ternary phase diagrams

Table 4: Investigation of the phase behaviour of various Smix ratios for a specific ME formulation.

Ratio of Smix: oil	Component percentage								
	oil	Smix (1:1)	Water	oil	Smix (1:2)	Water	oil	Smix (2:1)	Water
1:10	0.44	0.68	99.01	0.10	1.78	98.78	0.60	1.09	99.01
2:9	2.99	11.34	89.46	2.34	25.34	75.67	4.65	13.66	85.66
3:7	4.87	18.09	78.09	4.23	38.99	57.98	6.88	22.35	72.67
4:8	12.45	28.03	60.87	11.34	42.45	49.89	16.99	33.87	53.44
1:1	12.07	47.45	41.02	15.23	47.98	40.98	29.07	53.46	21.34
6:4	16.89	64.90	22.09	22.54	56.78	23.64	30.66	58.90	14.56
7:3	28	69.03	2,44	26.67	55.99	20.09	32.76	61.23	9.78
8:2	Milky solution			29.78	63.87	10.01	Viscous gel formulation		
10:1				33.76	67.08	1.99			

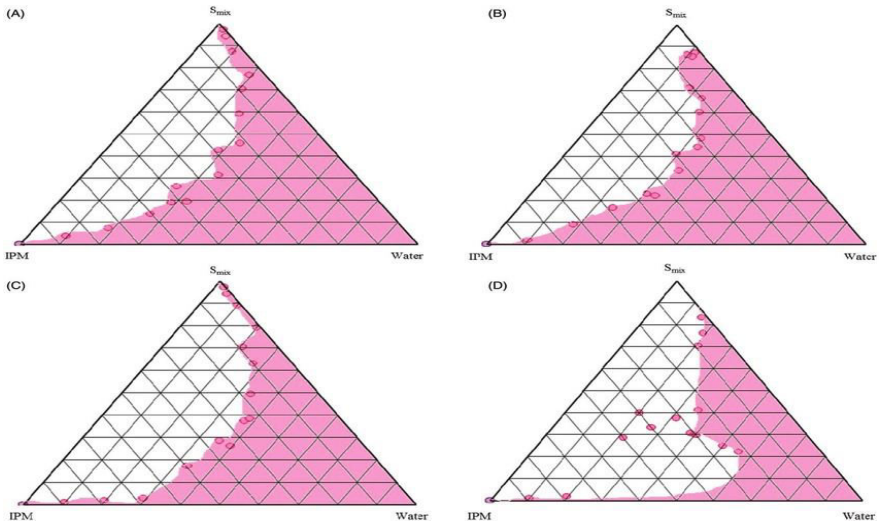

Figure4: Pseudo-ternary phase diagrams were constructed for PF loaded MEs consisting of oil (IPM), Smix (surfactant: Cremophor EL, co-surfactant: IPA), and water at different oil ratios. Smix ratios.

3.6 Examination of microemulsion formulation:

Table 5: Experimental trials of D-optimal design were conducted for FP microemulsion, and the resulting data were analysed for their responses.

Batch no.	Experimental no.	X1 (%)	X2 (%)	X3 (%)	Y1 (nm)	Y2 (mg/ml)
F1	1	0	1	0	31.44±1.55	41.7±2.45
F2	2	0	1	0	32.78±2.67	40. ±3.78
F3	3	1	0	0	20.34±1.34	38.99±2.89
F4	4	1	0	0	18.87±0.65	37.94±1.55
F5	5	0.5	0.5	0	34.23±1.56	38.77±4.67
F6	6	0.5	0.5	0	32.88±2.34	39±2.35
F7	7	0.778	0.298	0.163	25.43±1.99	30.77±3.78
F8	8	0.546	0.456	0.163	26.67±0.65	33.5±3.77
F9	9	0.289	0687	0.163	26.90±0.66	39.34±2.87

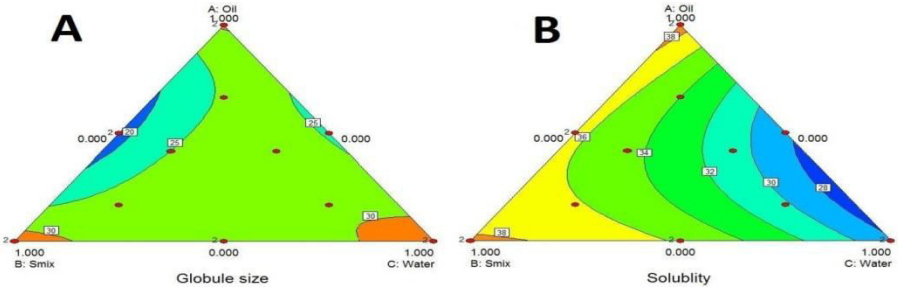

Figure 5: Optimization of PF microemulsion: contour plots of the D-optimal design A: the factors' effects on globule size (Y1) and B: the variables' effects on solubility (Y2).

Table 6: Summary statistics were generated for the measured responses of a D-optimal design for PF microemulsion.

Results	level	SD[a]	R^2	Adjusted R^2	PredictedR 2	PRESS
Y1	Linear	4.9	0.1644	0.030	-0.4140	501.10
	Quadratic	3.15	0.9087	0.7230	0.4830	188.90
	SpecialCubic	**1.5**	**0.9684**	**0.9280**	**0.8650**	**52.50**
	Cubic	1.87	0.9653	0.9333	0.608	146.20
Y2	Linear	2.8	0.7654	0.5616	0.4290	165.80
	Quadratic	**2.40**	**0.8125**	**0.715**	**0.6515**	**100.88**
	SpecialCubic	2.76	0.8130	0.6850	0.6110	115
	Cubic	1.10	0.9822	0.9522	0.6815	93.20

3.7 Physical and chemical analysis of ME

3.7.1 Microscopy for transmission electrons: The optimised ME globules, when seen under a transmission electron microscope in the absence of aggregation, had a virtually spherical form. The globule looked opaque and black when illuminated at high intensities (Figure 6). To improve the contrast and brightness, we utilised Adobe Photoshop CS2.

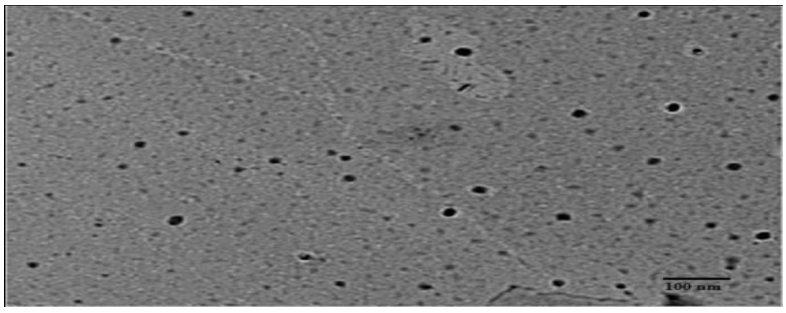

Figure6: Transmission electron microscopy (TEM) picture of a microemulsion loaded with optimised PF

Particle sizes averaged 18.62 nm, zeta potentials were -3.87, and PDIs were 0.14 for the optimised ME (Figures 7 and 8). The presence of a PDI score around zero indicates that the ME globules were somewhat homogeneous in size.

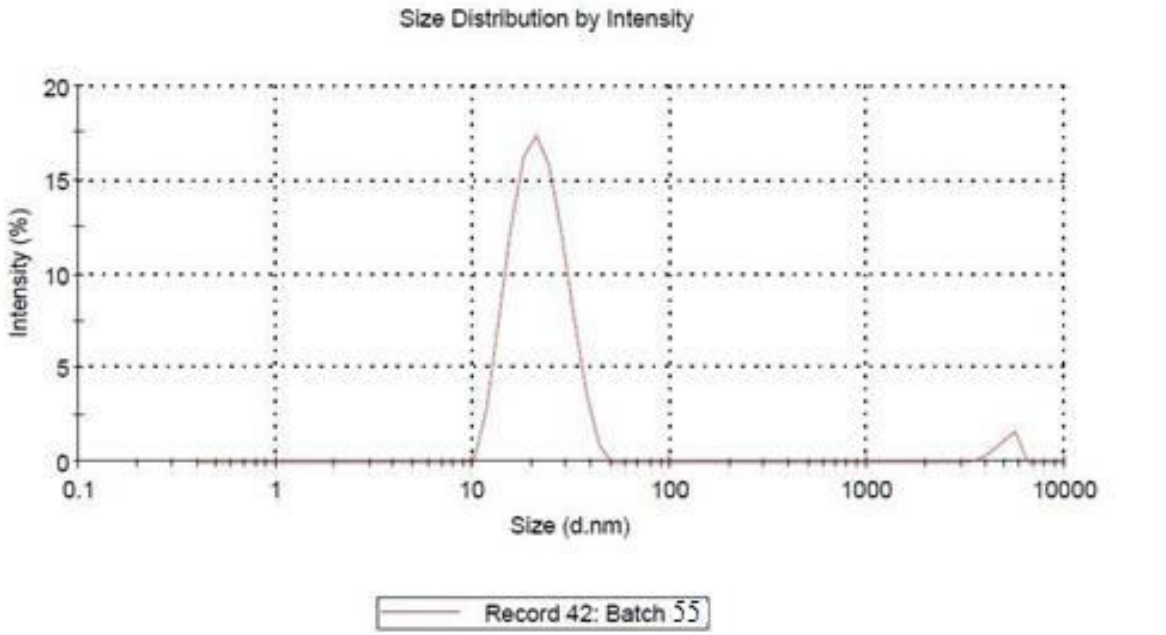

Figure 7: The microemulsion containing PF was analysed to determine the distribution of globule sizes.

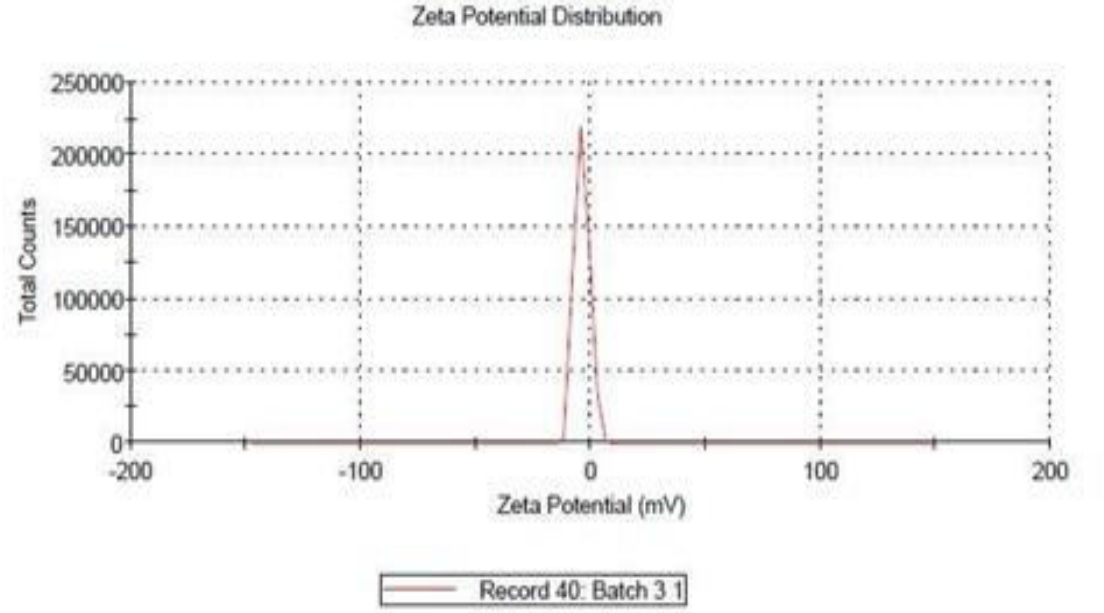

Figure 8: Distribution of zeta potential in microemulsion loaded with FP

Table 7: Physical and chemical properties of microemulsion.

Physical and chemical properties	Outcomes
PercentageTransmittance	>99.09%
Refractiveindex	1.45
Isotropicnature	Opticallyisotropic
Electricalconductivity	165.4±3.1µscm^{-1}
Viscosity	42.51±0.30 mPas
Typeof emulsion	O/W
pH	5.0- 7.0

3.7.2 Spreadability

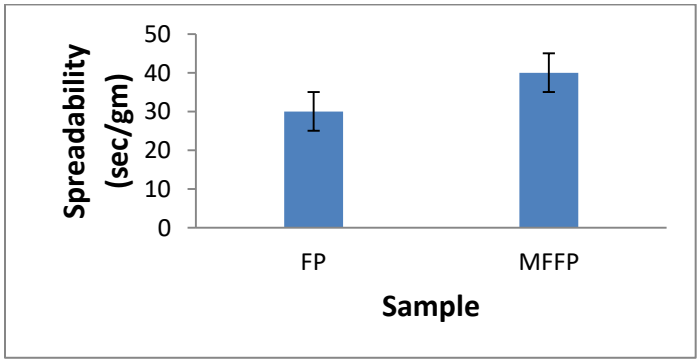

Figure 9: spreadabilityof FPloadedformulations

Table 8: RheologicalparametersofMFFPand FPM

Rheologicalparameters	MFFP (FP marketed formulation)	FPM (FPplaindrug)
Viscosity*(Pa-s)	27.70	15.30
Yieldstress(Pa)	35.45	19.70
Spreadability(sec/gm)	9.44±0.6	4.14±0.20
Drugcontent	99.8%	99.6%

Note:*Firstviscosityreadingwhentorqueexceeds10

3.7.3 Invitrorelease study of PF loaded formulations:

ME was tested for its ability to release drugs in vitro and contrasted with the traditional product Dermovate ®, which is available for purchase. Over the course of eight hours, ME displayed in vitro drug release that was both quicker and significantly greater than that of MFPF (the reference) at all sample locations (Figure 10). The ME released 83.35±2.12 µgcm-2 of FP while the MFPF released 71.45±1.5 µgcm-2 of FP after 8 hours of application. The first two have far

lower and much slower rates of release, which may indicate that the medicine is either kept in the dermal layer or on the skin's surface. This research indicates that an ex vivo permeability investigation was conducted [82].

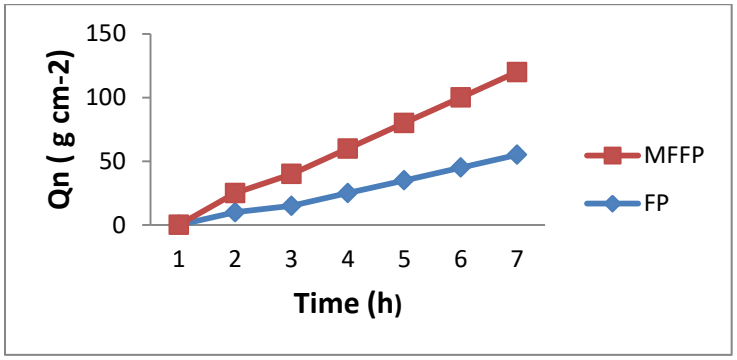

Figure 10: *Invitro*release profiles of tested formulations of PF(mean±SD,n=3);

3.7.4 Stability study of microemulsion:

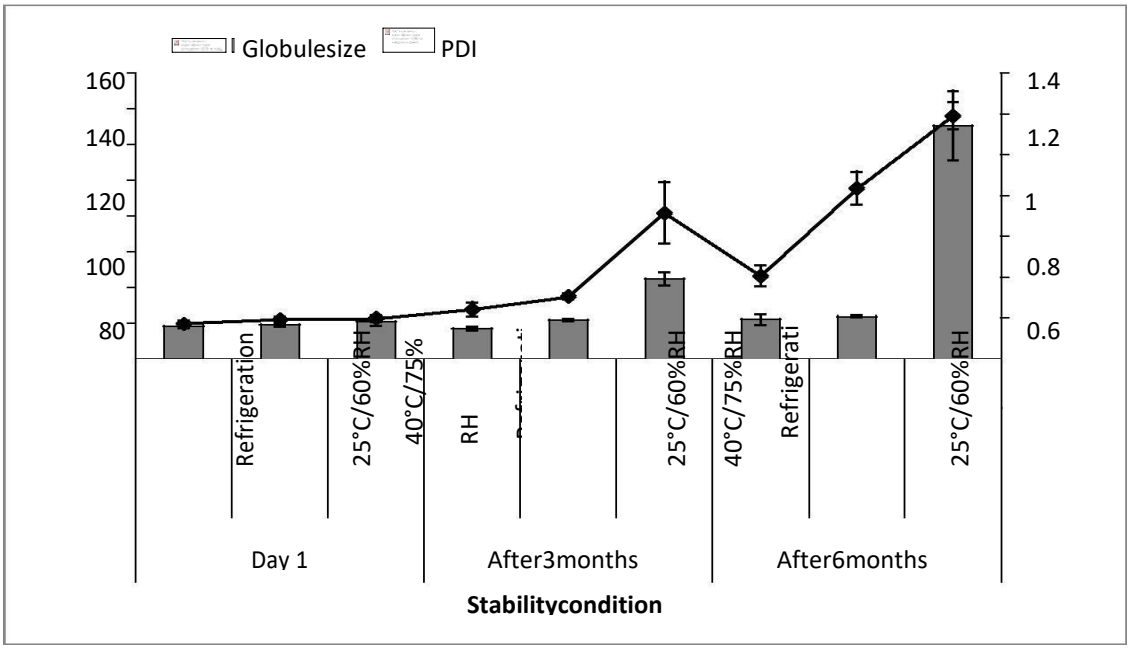

Figure 3.13:Stability investigations of ME (mean±standard deviation, n=3)

The thermodynamic stability of the dispersed systems was assessed by subjecting them to centrifugation and freeze-thaw experiments as stress conditions. No phase separation was seen in the optimised microemulsion when it underwent centrifugation at various temperatures and speeds. Phase separation was seen as an indication of the stability of the formulation. Due to the negative and low free energy of microemulsion generation, the formulations exhibited stability under stress [86].

Table 3.14: Stability study of FP loaded Microemulsion

Time	Condition of storage	Participation of drug	Creaming	Separation of phage	Centrifugation (100000 rpm)	Transmutation
1 day	Refrigeration	NO	NO	NO	One Phase	99.97±0.12
	25^0C/60% RH	NO	NO	NO	One Phase	99.50±o.45
	40^0C/75% RH	NO	NO	NO	One Phase	99.23±0.48
90 Day	Refrigeration	NO	NO	NO	One Phase	98.57±0.74
	25^0C/60% RH	NO	NO	NO	One Phase	97.23±0.32
	40^0C/75% RH	Yes	Yes	Yes	Two Phase	-
180 Day	Refrigeration	NO	NO	NO	One Phase	99,54±0.56
	25^0C/60% RH	NO	NO	NO	One Phase	98.85±0.65
	40^0C/75% RH	Yes	Yes	Yes	Two Phase	-

Conclusion:

Ultimately, the examination of Fluticasone Propionate (FP) using calibration data from different solvents and the formation of a microemulsion has shown its promise as a topical therapy owing to its ability to dissolve and maintain stability. The calibration curves in phosphate buffer solutions, methanol, and menthol demonstrated a strong linear correlation between absorbance and concentration (R^2=0.999), underscoring the need of accurate analytical techniques. The research emphasized that FP has a high solubility in organic solvents but a low solubility in water, which means that appropriate delivery strategies are needed to improve its bioavailability. The optimised microemulsion, composed of Isopropyl Myristate (IPM), Cremophor EL, and Isopropyl Alcohol (IPA), was selected based on its favourable solubility characteristics and its capacity to improve skin permeability. Compatibility tests have verified the durability of the formulation, while pseudo-ternary phase diagrams have determined the ideal Smix ratios, leading to the creation of a reliable and enduring microemulsion with an average particle diameter of 18.62 nm and a polydispersity index of 0.14. The stability and isotropic nature of the microemulsion were confirmed via other physical and chemical analyses, such as conductivity, viscosity, and refractive index tests. These findings provide further evidence of the microemulsion potential effectiveness in clinical applications.

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