Drug Development and Research©
16 (2) 2024 : 001-007 • RESEARCH ARTICLE

Formulation of baclofen microemulsion and validation of analytical method for quantitative estimation by UV spectroscopy

Patidar Mohini*, Pillai Sujit, Deshmukh Nitin, Patel Sumit, Mahajan Aakansha

Department of Pharmaceutical Analytical Science, GRY Institute of Pharmacy, Borawan, India

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

ABSTRACT

Baclofen is a centrally acting skeletal muscle relaxant used to treat muscle spasticity and multiple sclerosis. Baclofen hydrophilic characteristics make it challenging for it to cross the blood brain barrier, resulting in a bioavailability of less than 60%. The current study's objectives are to develop, optimize and validate an analytical method for the quantitative estimation of Baclofen by UV-visible spectrophotometer in accordance with ICH guidelines, as well as to improve the bioavailability and efficacy of drug release by formulating micro emulsion of Baclofen. Four different batches were formulated on the bases of S/Cos ratios 3:1, 3.5:1, 4.5:1 and 1.5:1 respectively by water titration method. Tween 80, span 80 and PEG 400 were blended together to form a homogeneous mixture, Baclofen was dissolved in oil phase. Oil phase and surfactant mixture were mixed slowly with continuous trituration. Drop wise additions of water were made to the existing mixture, which was stirred for 30 minutes at 3000 rpm on a magnetic stirrer. The result of FTIR study were indicated compatibility in between Baclofen and excipients. On the bases of solubility studies 0.1 N NaOH was selected for analytical method validation. The λ_{max} and regression equation found to be 221 nm and Y=0.0603x+0.0207, R^2=0.999. The result of all analytical validation parameters was not exceeding by 2% RSD value. Out of all batches M1 shows more transparent, no phase separation, pH of 6.7, particle size 100 nm, low viscosity and 96.73% drug content value. It exhibited good stability over the course of the six month stability tests, with no significant changes in its physicochemical characteristics. Hence, it was concluded that the micro emulsion formulation of Baclofen is a potential method for oral delivery that will increase bioavailability.

Keywords: Baclofen; Micro emulsion; Analytical method; 0.1 NaOH; Tween 80; Castor oil; Polyethylene glycol

Abbrevations: NDDS: Novel Drug Delivery System; FTIR: Fourier Transform Infrared analysis; UV spectroscopy: Ultra Violet spectroscopy; LOD: Limit of Detection; LOQ: Limit of Quantitation; SD: Standard Deviation; RSD: Relative Standard Deviation of the Response; σ: Slope of the calibration curve; PEG: Polyethylene Glycol

Address for correspondence:

Patidar Mohini,
Department of Pharmaceutical Analytical Science,
GRY Institute of Pharmacy, Borawan, India
E-mail: mohinipatidar7@gmail.com

Word count: 3266 **Figures:** 06 **Tables:** 05 **References:** 18

Received: 14.06.2023, Manuscript No. IJDDR-23-13889; **Editor assigned:** 17.06.2023, PreQC No. IJDDR-23-13889 (PQ); **Reviewed:** 02.07.2023, QC No. IJDDR-23-13889; **Revised:** 05.03.2024, Manuscript No. IJDDR-23-13889 (R); **Published:** 12.03.2024

INTRODUCTION

The term NDDS refers to entirely novel, innovative approaches for effectively delivering pharmaceutical compounds inside the body as needed to achieve their desired beneficial effects. Site targeting within the body might be a part of it. It frequently worries about both the quantity and frequency of consumption of drugs. Drug delivery is a term that directly pertains to dosage and administration method. The goal of NDDS is to specifically target a medication to the necessary tissue while also improving medication potency, controlling medication release to ensure a continued beneficial impact and providing higher safety [1].

A micro emulsion was first proposed by Hoar and Schulman in 1943. A type of NDDS technological advances is micro emulsion [2]. Micro emulsions are liquid combinations of oil, water and a surfactant that are transparent, stable and isotropic, typically in combination with another surfactant called a co-surfactant. The "oil" may actually be a complex blend of various hydrocarbons and olefins, while the aqueous phase may also contain salt(s) and/or other substances. Micro emulsions do not require the high shear conditions that are often employed to create conventional emulsions, in contrast to ordinary emulsions and they develop simply by mixing the components. Oil distributed in water is known as a direct micro emulsion and water dispersed in oil is known as a reverse micro emulsion. When two immiscible phases (water and "oil") are present with a surfactant in ternary systems like micro emulsions, the surfactant molecules may form a monolayer at the interface between the oil and water. Small droplets or particles in the dispersed phase typically range in size from 10 to 200 nm [3,4].

Classification of micro emulsion

Winsor identified four different types of micro emulsion phases that are present in equilibrium and are referred to as Winsor phases.

Winsor I (two phase system): Upper oil layer and lower (o/w) micro emulsion phase are in equilibrium.

Winsor II (two phase system): The upper (w/o) micro emulsion and lower surplus water are in equilibrium

Winsor III (three phase system): Middle bi-continuous phase of o/w and w/o, also known, is in equilibrium with upper phase oil and lower phase water.

Winsor IV (single phase system): It creates a uniform mixture of oil, water and surfactant [5].

Micro emulsions are superior to traditional emulsions, suspensions and micelles solutions as well as the colloidal systems under examination and they may provide other carriers. They are promising delivery methods that enable prolonged or controlled release for the administration of medications *via* percutaneous, oral, topical, transdermal, visual and parenteral routes. They benefit from spontaneous synthesis, simplicity in manufacturing and scalability, thermodynamic stability, increased hydrophobic drug solubilisation in medications and bioavailability [6].

Baclofen (γ-amino-β-[p-chlorophenyl]-butyric acid) is a centrally acting skeletal muscle relaxant derived from the inhibitory neurotransmitter γ-Amino Butyric Acid (GABA). It is used to treat muscle spasticity, especially in patients with multiple sclerosis or with spinal or cerebral disorders [7].

Baclofen has hydrophilic properties and does not readily cross the blood brain barrier, because of this it's has less than 60% oral bio availability. The h alf-life i s 2 -6 hours a fter o ral a dministration. 70%-80% of Baclofen is eliminated in an unchanged form by renal excretion. Drug concentrations of Baclofen in the cerebrospinal fluid are approximately 8.5 times lower than in the plasma due to this it is prescribed to take TDS. In market Baclofen is available in tablet, solution, packet and suspension formulations [8].

In this study, a Baclofen o/w micro emulsion was created using polymer, oil and surfactant to increase bioavailability and improve drug absorption across biological membranes. Low viscosity micro emulsions have greater absorption into the body, less surfactant content decreases negative effects and prevent first pass metabolism which increases the bioavailability of the drug. As a less cost, more easily scaled up option to the traditional oral, micro emulsion formulation can be formulated.

A number of analytical methods were available to assess the purity of the drug Baclofen through UV spectroscopy by using different solvents. Another goal of this study to develop and optimize a new analytical method which is quick, simple, precise, sensitive and cost effective for estimating Baclofen using a UV-visible spectrophotometer.

MATERIALS AND METHODS

Instrumentation

UV-1800 Shimadzu with UV probe software system were utilized for qualitative determination of baclofen, digital pH meter, laboratory centrifuge, brookfield viscometer, stage microscope, magnetic stirrer, pycnometer.

Reagents and chemicals

Baclofen was purchased from Yarrow Pharma Mumbai, Tween 80 was purchased from Sd Fine chemicals Ltd, Ahmadabad, Span 80 and PEG 400 was purchased from Loba chemicals Ltd Mumbai, castor oil was purchased from gliter pharmaceutical Rangwasa, Rao, Each of the ingredients and chemicals are an analytical grade. They were procured from the GRY institute of pharmacy's laboratory in Borawan, India.

Pre formulation studies

Drug excipients compatibility study: FTIR is an effective method for examining the interaction between drugs and excipients. Surfactant, co-surfactant and oil were added to the pure medication individually then KBr pellets are prepared and the resulting mixture was scanned in the 400 cm^{-1}–4000 cm^{-1} range. To reduce the possibility of significant functional groups in the drug interacting with the excipients, the comparison was conducted using the FTIR spectrum of the pure drug [9].

Drug solubility analysis: A solubility analysis was carried out in order to create a new analytical method. Baclofen powder was added in excess to the solvents water, ethanol, methanol, 0.1 N HCl and 0.1 N NaOH and the mixture was then vortexes. The samples were left at room temperature for 30 minutes to achieve equilibrium. The un-dissolved drug was subsequently removed from the equilibrated samples using sonication for 30 minutes. Then filter the solution by Whatman filter paper. Before formulating micro emulsion choose appropriate oil, surfactant, and co surfactant in which drug shows maximum solubility. The same approach was conducted to check the solubility of Baclofen in different oil, surfactants and co surfactants.

Description of analytical method

Selection of wavelength: 100 mg pure Baclofen was dissolved in 100 ml of 0.1 N NaOH solution to create a primary stock solution with a concentration of 1000 µg/ml. This solution was further used to determine the wavelength of maximum absorption (λ_{max}) of baclofen. Then, 10 ml of primary stock solution was diluted with 100 ml of 0.1 N NaOH solution to make a concentration 100 µg/ml secondary stock solution. Different concentrations of the drug dilution (2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml) were prepared with the same solvent and then scanned with a UV-visible spectrophotometer between the wavelengths of 200 nm-400 nm with a 0.1 N NaOH solution serving as a blank.

Validation of analytical method

Analytical method for Baclofen is validate as per ICH guideline. The main validation parameters such as linearity and range, accuracy and precision, recovery, ruggedness, LOD and LOQ were evaluated in developed method [10-13].

Accuracy: From the stock solutions 4, 6 and 8 µg/ml concentration dilution were made in 0.1 N NaOH and samples were scan at 221 nm to measure the accuracy. From the absorbance value % purity was determined and calculates SD and RSD value.

Precision: The precision was determined in the terms of repeatability, intermediate and reproducibility. 4, 6 and 8 µg/ml concentration solutions was analysed to determine all parameter and the relative standard deviation was calculated.

Linearity: A series of dilutions of Baclofen at 1, 2, 3, 4, 5, 6, 7, 8 and 10 g/ml were made and then scanned under a UV light. A calibration curve was created using the resulting absorbance data. Further calculations were made by Y-intercept equation's correlation coefficient.

Determination of LOQ and LOD: LOD and LOQ were determined to determine the proposed method's sensitivity. The lowest amount of analyte quantify is LOQ, whereas LOD is the lowest amount of analyte detectable by the technique. The ICH recommendations were used to compute the baclofen LOD and LOQ using the formulas LOD=3.3 /S=0.825 g/ml and LOQ=10 /S=2.5 g /ml.

Range: By comparing the results interval of lower and upper levels of LOD, it has been possible to define the range of analytical methods with a reasonable degree of precision and accuracy.

Robustness: The ability of an analytical method to stay unaffected by slight but intentional changes in the method parameters is measured as robustness, which gives a clue as to how reliable the method will be in typical conditions. The robustness of this method was determined by analyzing of 3 µg/ml and 6 µg/ml concentration solutions within the day and calculating SD and RSD.

Ruggedness: The robustness of this procedure was assessed by two analysts analyzing solutions with concentrations of 5 µg/ml and 10 µg/ml on the same equipment. After that, SD and RSD were calculated.

Formulation of micro emulsion

Castor oil and sesame oil were chosen as the oil phases for the creation of the o/w micro emulsion based on the solubility investigation of the drug Baclofen. Tween 80 and span 80 mixture together used as surfactants and co surfactants; propylene glycol is used as the polymer and distilled water as the aqueous phase. Four surfactant-co surfactant ratios (S/Cos ratios) batches, including 3:1, 3.5:1, 4.5:1 and 1.5:1, were tested in the current study. To make a micro emulsion, Baclofen were dissolved in oil phase and Surfactant, co surfactant and PEG was blended together to form a homogeneous mixture (Smix). Oil phase and Smix phase were mixed slowly with continuous trituration. Water was added drop in drop to the present mixture which was mixed on a magnetic stirrer at 3000 rpm at for 30 minutes. The slow and continuous stirring allows equilibration between oily and aqueous phases. The resulted mixtures ranged from a milky white, highly turbid, translucent, and transparent liquid phase. The formation of transparent, free-flowing mixtures indicated the endpoint of the titration. The percentage of four different phases oil, water and mixture of surfactant and co surfactant were calculated [7].

Evaluation parameters of baclofen microemulsion

Optical transparency: After each addition of water, the mixture of oil, surfactant, or surfactant and co-surfactant was visually inspected. By visual inspection formulation's colour, phase separation, creaming and clarity were examined [14].

Viscosity measurement: Using a brook field viscometer, the optimized formulation's viscosity was assessed without dilution (DV-E Brookfield Viscometer Model-LVDVE). 500 ml sample formulation was keeping in beaker, at 350°C ± 2 room temperature and spindle no. 6, 7 at 60 rpm was used to measure the viscosity at. For reproducible results, these processes were repeated three times.

Particle size determination: The stage microscopic method is used to determine particle size. In this technique, a created micro emulsion droplet was placed on a piece of glass using a stage microscope. A 100X eyepiece lens was used to observe the droplet's size and then particle size calculated [15].

Specific gravity: The density of the micro emulsion and the water was obtained by using a density bottle and the specific gravity of the micro emulsion was then calculated using the formula [16].

pH determination: The pH of the micro emulsion obtained was measured using a digital pH meter at 25°C and calibrated with phosphate buffer. For greater accuracy, every reading was obtained in triplicate and the estimate of the triplicates was obtained [17].

Drug content analysis: 5 ml drug micro emulsion was dissolved in 100 ml of 0.1 N NaOH, shake the solution till the micro emulsion is completely mixed, then kept in centrifugation tube at 3000 rpm for 30 mins. The excess was divided and filtered. From this solution 0.1 ml solution was diluted to 10 ml with same solvent then again filtered it. The absorbance was measured at 221 nm by UV Spectrophotometer using the placebo micro emulsion as a blank solution and the drug content was calculated.

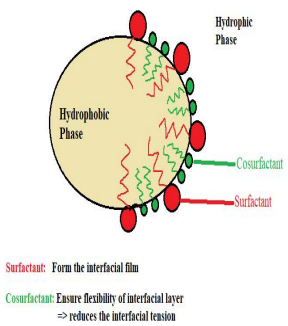
Stability testing: According to ICH guidelines, the accelerated ambient stability investigation was carried out in stability chambers (Thermo laboratories) at temperature at 40 ± 2°C, 25°C and 10°C, respectively and humidity (75 ± 5% RH). The formulation was kept in a hermetically screw capped bottle with a volume of around 100 ml. In order to evaluate the physical appearance, phase separation at accelerated gravity and drug content during the course of the study's 6 month duration, sample analysis were taken in three month intervals [18].

RESULTS AND DISCUSSION

Interpretation of IR spectra of baclofen and other excipients

Characteristic absorption bands in the IR spectra of baclofen can be identified. They are connected to stretching vibrations of the N-H group of primary amines (3447.89 cm^{-1}), stretching vibrations of the C-Cl group (664.48 cm^{-1}) and different COOH group (1729.65 cm^{-1}) vibrations. The IR spectra of combinations of baclofen with tween 80, span 80, PEG 400, castor oil and honey contain those particular bands. There has been no change in the chemical structure of baclofen or its compatibility with other substances, as evidenced by the presence of all typical bands of the drug and excipients in the IR spectra of combinations with varied concentrations of both components (Fig. 1. and Tab. 1.).

Fig.1. Structure of micro emulsion.



Tab. 1. Peaks observed in infrared spectrum of baclofen.	Wave number (cm^{-1})	Corresponding functional group and type of molecular vibration
	1527.15	Aromatic C=C (S)
	2817.44	Alkane (S)
	3447.89	Amine N-H (S)
	664.48	Halogen C-Cl (S)
	1729.65	Carboxylic acid C=O (S)

Solubility

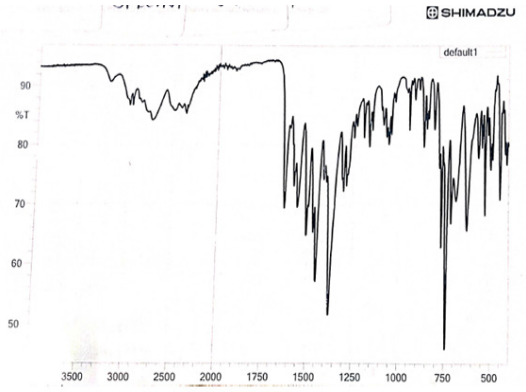
Baclofen shows better solubility with 0.1 N NaOH so it is used as solvent for analytical method development (Tab. 2.).

Tab. 2. Solubility study.	Solvent	Solubility
	Water	Slightly soluble
	Ethanol	Partial soluble
	Methanol	Partial soluble
	0.1 N NaOH	Soluble
	0.1 N HCl	Soluble

Analytical method results

Different dilutions ranging from 2 g/ml to 10 g/ml were prepared for the purpose of determining the analytical wavelength and scanned at wavelengths between 200 and 400 nm in a UV visible spectrophotometer. Maximum absorbance was detected in the dilutions at 221 nm. Consequently, 221 nm was chosen as the analytical wavelength (Fig. 2.)

Fig.2. Baclofen IR spectrum.



Validation of analytical method

Analytical method was validated as per ICH guideline. According to the results of linearity value concentration range from 1 µg/ml to 10 µg/ml, correlation coefficient equation found to be y=0.0603 X+0.0207 and regression value found to be R^2=0.999 (Fig. 3. and Fig. 4.). Accuracy, precision, robustness and ruggedness were calculated and result value of the relative standard deviation was not exceeding by 2%. Results of LOD LOQ, range were 0.825 µg/ml, 2.5 µg/ml, 1 µg/ml, 10 µg/ml respectively (Tab. 3.).

Fig.3. Calibration curve results.

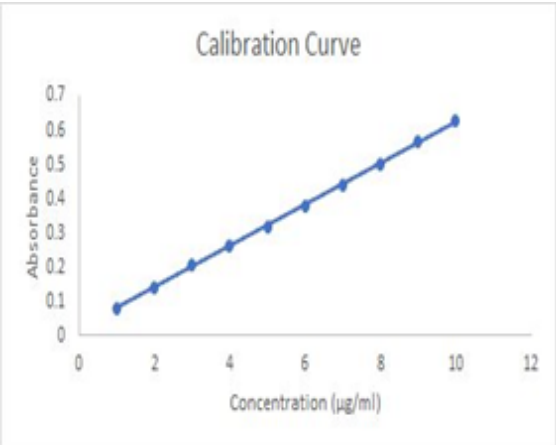
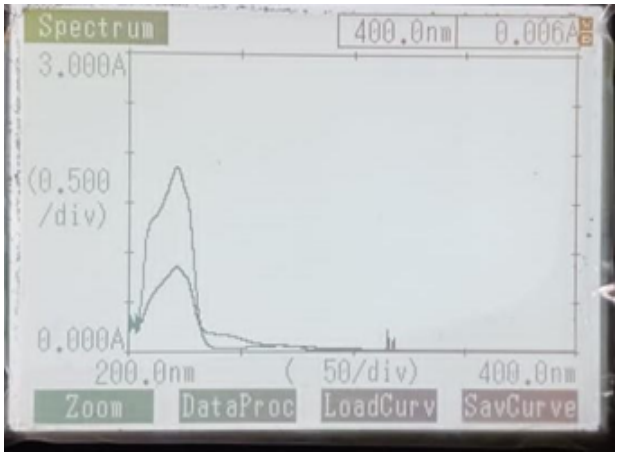


Fig.4. UV spectrum of Baclofen in 0.1 N NaOH solvent.



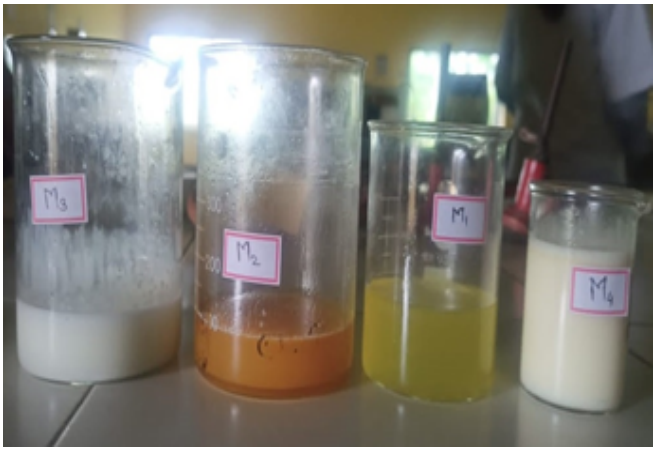
Tab. 3. Summary of validation parameters.

S. no.	Parameter	Results
1	λ_{max}	221 nm
2	Regression equation (y=mx+c)	Y=0.0603x+0.0207
3	Slope	0.0603
4	Intercept	0.0207
5	Correlation coefficient (R^2)	0.9995
6	Accuracy (RSD)	Less than 2%
7	Interday precision (RSD)	Less than 2%
8	Intraday precision (RSD)	Less than 2%
9	Linearity range	1 µg/ml-10 µg/ml
10	LOD	0.825 µg/ml
11	LOQ	2.5 µg/ml
12	Ruggedness1	Less than 2%
13	Ruggedness2	Less than 2%
14	Robustness	Less than 2%
15	% Purity of formulation	99.30%

Composition formula optimization

Span 80 has a low HLB value with lipophilic properties, which can be used to form oil-in-water micro emulsions when used in combination with tween 80 having hydrophilic properties and high HLB value. The emulsifier's tween 80 and span 60 are frequently used in combination. In comparison to using only one surfactant, the combination of these two surfactants can increase the solubility of drug in water and physical stability of the micro emulsion. PEG-400 was used as co solvents and polymer for improving the aqueous solubility of weakly water soluble Baclofen which will help in improving drug bioavailability. Four different composition formulas were optimized for fixing the S/Cos ratios (Fig. 5.). Out of four formulas M1 appear as clear, thermodynamically stable isotropic liquid mixtures of oil, water and surfactant and their result of evaluation are mentioned below (Tab. 4.).

Fig.5. Baclofen micro emulsion formulations.



Tab. 4. Composition formula of baclofen micro emlusion.

Ingredients	Formulation code (100 ml)				Purpose
	F1	F2	F3	F4	
Baclofen	100 mg	100 mg	100 mg	100 mg	Drug
Tween 80	30 ml	33 ml	28 ml	32 ml	Surfactant
Span 80	10 ml	6 ml	13 ml	10 ml	Co-surfactant
PEG 400	8 ml	8 ml	8 ml	10 ml	Polymer
Sesame oil	-	32 ml	16 ml	14 ml	Oil phase
Castor oil	32 ml	-	16 ml	16 ml	Oil phase
Rose water	4 ml	5 ml	3 ml	4 ml	Fragrance
Water	16 ml	16 ml	16 ml	16 ml	Aqueous phase

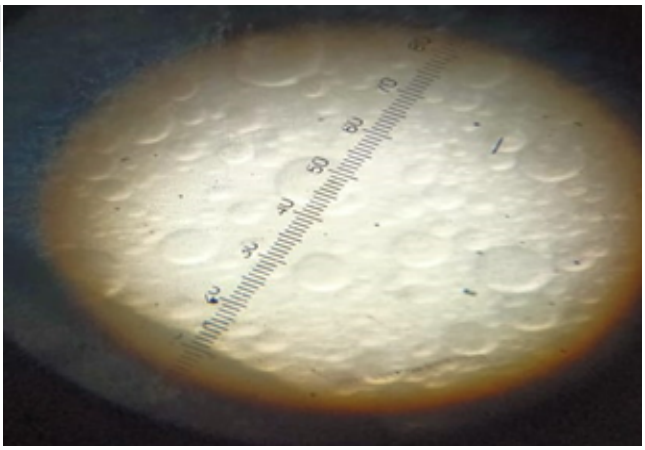
Evaluation of formulation

Optical transparency: Micro emulsions are regularly inspected to check the formulation's color change, phase separation in oil and water phase, upward and down ward creaming. Through the examination of physical parameter it was concluded that there is no colour change and creaming of formulation's found. Both the phase's oil and water were immiscible with each other. Micro emulsion of Baclofen M1 was transparent and cleared solution.

Viscosity measurement: Using a Brookfield Viscometer, all the formulation's viscosity was assessed at 35°C ± 2°C room temperature and 60 rpm. Viscosity of formulation M1 and M4 were found to be 82 and 110 dynes/cm^2.

Particle size determination: The rate of phase separation is directly propositional to the radius of the globules. The particle size of the formulation found to be in between 100 nm-125 nm, acceptable range (Fig. 6.).

Fig.6. Baclofen micro emulsion particle size.



Specific gravity: The density of the micro emulsion was calculated as compared to water. The specific gravity of the micro emulsion was found to be 0.89-1.00, equivalent to water.

pH determination: The pH of the micro emulsion was measured using a digital pH meter. The pH of the formulation M1 found to be 6.7, which in slightly acids in nature.

Drug content analysis

For each batch of formulation, drug content studies were completed in triplicate. The calculated drug content was found to be in range of 89.19% to 96.73%. According to the data, formulation M3 has the least drug, whereas formulation M1 contains the highest amount shown in (Tab. 5.).

Tab. 5. Result of evaluation parameters of baclofen micro emulsion.

Parameters	Formulations			
	M1	M2	M3	M4
Phase separation	No	No	Yes	Yes
Clarity	Transparent	Milky	Milky	Milky
Colour	Yellowish	Brown	White	Whitish brown
Viscosity (dynes/cm^2)	82	87	95	110
Particle size(nm)	100	110	118	125
Specific gravity	1	0.89	0.8	0.6
pH	6.7	6.2	6.4	6.5
Drug content	96.73%.	90.32%	89.19%	92.45%

Stability testing

The stability study was carried out to refine the ideal micro emulsion formulation for harsh environments. After 3 month periods sample was collected and evaluated. Drug content, pH and viscosity of best formulation M1 was 95.98%, 6.6 and 81.4 respectively. There is no phase separation, cracking and coalescence was examined in the samples.

CONCLUSION

A micro emulsion of baclofen was successfully formulated. Micro emulsions have improved the bioavailability, effectiveness, and rate of absorption of Baclofen in accordance with the objectives of the current investigation. The optimized formula consists of Tween 80, span 80 and PEG 400 in (3:1) ration. A FTIR investigation found that the excipients and the medication were compatible. Utilising 0.1 N NaOH solution the analytical method was validated and It was accurate, precise and economical. M1 batch had all the desired characteristics and a drug content of 96.73% across all batches. On the bases of results, it was concluded that the micro emulsion formulation of Baclofen is a potential and effective formulation for oral delivery that will increase bioavailability.

ACKNOWLEDGEMENTS

Without the assistance of Dr. Sujit Pillai, Mr. Sumit Patel, Ms. Aakansha Mahajan and my family, this research would not have been feasible. I'd like to take this initiative to thank GRY Institute of Pharmacy for providing the required equipment and materials to enable me to conduct the research project.

REFERENCES

1. **Chauhan L, Thakur P, Sharma S.** Microemulsions: New vista in novel drug delivery system. *Innov Pharm Pharmacother*. 2019; 7:37-44.
2. **Gibaud S, Attivi D.** Micro emulsions for oral administration and their therapeutic applications. *Expert Opin Drug Deliv*. 2012; 9:937-51.
3. **Madhav S, Gupta D.** A review on micro emulsion based system. *Int J Pharm Sci Res*. 2011; 2(8):1888-1199.
4. **Saini JK, Nautiyal U, Kumar M, et al.** Micro emulsions: A potential novel drug delivery system. *Int J Pharm Sci Res*. 2014;2:15-20.
5. **Jadhav A, Daundkar A, Morale D, et al.** Review on: Micro emulsion a novel approach for drug delivery. *Int J Pharm Sci Rev Res*. 2018;11:60-65.
6. **Katiyar BS, Katiyar SS, Mishra PS, et al.** Micro emulsions: A novel drug carrier system. *Int J Pharm Sci Rev Res*. 2013;20:138-148.
7. **Adhao VS, Thenge RR.** Development and validation of stability indicating high performance liquid chromatography method for determination of baclofen. *Res Artic American J Pharm Tech Res*. 2017;7:544-556.
8. **Rojek B, Wesolowski M, Suchacz B.** Detection of compatibility between baclofen and excipients with aid of infrared spectroscopy and chemo metry. *Spectrochim Acta A Mol Biomol Spectrosc*. 2013;116:532-538.
9. **Potdar M.** Pharmaceutical quality assurance. *Nirali prakashan*. 2017;6: 8.29-8.31.
10. **ICH Harmonised Tripartite Guideline**. Validation of analytical procedures: Text and methodology, Geneva: IFPMA. 1996;1-5.
11. **Gabhane KB, Jaiswal A, Tapae KK.** Simple and validated ultraviolet spectrophotometric method for the estimation of baclofen in bulk form. *Res J Pharm Biol Chem Sci*. 2014;5:104-109.
12. **Lotfi B, Ghorbel A, HassineT.** Baclofen pharma profile. Article in compendium yardley, PA. 2007:629-632.
13. **Katiyar B, Katiyar S.** Micro emulsions: A novel drug carrier system. *Int J Pharm Sci*. 2013;20:138.
14. **Gui Sh Y, Wu L, Peng DY, et al.** Preparation and evaluation of a micro emulsion for oral delivery of berberine. *Pharmazie*. 2088;63: 516–519.
15. **Yadav V, Jadhav P, Kanase K, et al.** Preparation and evaluation of microemulsion containing antihypertensive drug. *Int J Appl Pharm*. 2018;10:138-146.
16. **Panghal A, Sachdeva M, Agarwal V.** Formulation and development of baclofen micro emulsion incorporated into transdermal patch. *J Drug deliv Ther*. 2022;12:55-63.
17. **Nath R, Bhowmik R, Chakraborty R, et al.** Preparation and evaluation of a novel oral microemulsion drug delivery system for enhancing the bioavailability of Diltiazem. *Int J Pharm Sci Rev Res*. 2021;70:164-170.
18. **Badawi A, Nour S, Sakran W, et al.** Preparation and evaluation of micro emulsion systems containing salicylic acid. *AAPS Pharm Sci Tech*. 2009;10: 1081-1084.