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# Formulation and *In Vitro* Evaluation of Brimonidine Tartrate Microemulgel for Topical Delivery

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**Abstract:** This research focuses on the formulation and evaluation of a novel micro-emulgel containing Brimonidine tartrate, a selective α2 adrenergic receptor agonist approved for treating facial erythema associated with rosacea. The poor aqueous solubility and BCS class-II classification of Brimonidine Tartrate often lead to limited efficacy and bioavailability, prompting the development of innovative formulations to enhance therapeutic outcomes. Brimonidine Tartrate exhibited the highest solubility in orange oil among the available oil phases. Tween 80 and Propylene glycol were identified as suitable surfactant and co-surfactant, respectively, based on their compatibility ratios. Formulations M-6 to M-9 were selected through physical inspection, drug content assessment, and globular size analysis. These microemulsions were then incorporated into a 1% Carbopol 934 and Carbopol 940 gel base, with Triethanolamine used for pH adjustment. The resulting formulations (MEG-1 to MEG-8) underwent a comprehensive evaluation, including physical examination, pH measurement, drug content determination, spreadability analysis, rheological study, *in vitro* % drug release study, and stability assessments. Among the eight formulations, MEG-3 emerged as the optimized formulation based on the acquired data. Formulation MEG-3 demonstrated a maximum drug release of 91.7% within 7 h, highlighting its potential for sustained and effective delivery of Brimonidine Tartrate. This study provides valuable insights into the development of an optimized microemulgel formulation, offering an enhanced approach for the topical delivery of Brimonidine tartrate. The promising results suggest potential applications in the management of rosacea-associated facial erythema, addressing the current challenges related to limited drug efficacy and bioavailability in existing treatments.

**Keywords:** Brimonidine tartrate, Microemulsion, Microemulgel, Pseudo-ternary phase diagram

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## Introduction

The integration of microemulsion technology into a gel base, forming microemulgels, represents a promising avenue for overcoming challenges associated with topical drug delivery. Microemulgels offer a synergistic solution to enhance bioavailability and efficacy, specifically

addressing issues related to drug penetrability and solubility. In this context, Brimonidine Tartrate, a potent α2 adrenergic receptor agonist known for its ability to induce vasoconstriction in small arterioles, emerges as a key candidate for treating rosacea-- a chronic skin inflammatory condition affecting the central facial area (Khullar *et al.,* 2012).

Rosacea's early manifestations include redness on the nose, cheeks, chin, or forehead, which, if left untreated, can progress to exhibit visible blood vessels, swelling, and acne-like exanthema. Leveraging the advantages of topical drug delivery becomes crucial in managing such localized skin disorders. By circumventing the challenges of first-pass metabolism, gastrointestinal degradation, and potential irritation associated with oral administration, the proposed microemulgel formulation seeks to optimize the therapeutic potential of Brimonidine tartrate.

Microemulgels, characterized by droplet sizes ranging from 10 to 100 nm, leverage the thermodynamic stability of microemulsions. This unique composition accommodates both hydrophilic and hydrophobic drugs, offering a versatile platform for effective drug delivery. The incorporation of non-polar oils, aqueous components, surfactants, and co-surfactants plays a pivotal role in overcoming the inherent limitations of hydrophobic drug solubility. The inclusion of surfactants in the immiscible oil and water phases reduces interfacial tension, fostering homogenous dispersion of hydrophobic drugs in the aqueous phase (Thakkar *et al.,* 2011).

This innovative approach not only addresses solubility barriers but also enhances drug release from the gel base, ensuring optimal therapeutic outcomes. By combining the advantages of microemulsion technology with the ease of application provided by gels, this proposed formulation holds significant promise for advancing the treatment of skin disorders, particularly rosacea.

This research focuses on the formulation and evaluation of a novel micro-emulgel containing Brimonidine tartrate (BT), a selective α2 adrenergic receptor agonist approved for treating facial erythema associated with rosacea.

## Materials and Methods

### *Formulation and Development of Microemulsion*

#### *Screening of formulation components by solubility studies*:

The methodical selection of components for microemulsion formulation involved a thorough screening process to ensure the safety, pharmaceutical grade, and skin-friendly characteristics of the chosen substances. These selected components are classified within the Generally Recognized as Safe (GRAS) category, validating their appropriateness for use. Surfactants were specifically chosen based on their Hydrophilic Lipophilic Balance (HLB) values, ensuring not only their effectiveness but also their non-toxic nature. The co-surfactant was meticulously chosen to establish a stable microemulsion with the surfactant at a minimum concentration, thereby enhancing the overall stability of the formulation (Patel, 2012).

The screening procedure encompassed various oils, including Orange oil, Light liquid paraffin, Sesame oil, Sunflower oil, Soybean oil, and Isopropyl myristate, along with surfactants such as Tween 80 and Tween 20, and co-surfactants like Propylene Glycol, Span 80, Span 20, and PEG 400. The solubility of Brimonidine Tartrate in each component was evaluated using the shake flask method. Excess amounts of the drug were introduced to 5 ml of each oil, surfactant, and co-surfactant, creating suspensions that underwent agitation on a mechanical shaker under ambient temperature and humidity conditions for 48 h at 100 rpm (Srinivas and Sreeja, 2013).

Following the agitation period, the suspensions were meticulously filtered through membrane filters and diluted with methanol. The quantification of Brimonidine Tartrate was achieved using a UV-visible spectrophotometer at

Table 1: Formulation of Brimonidine tartrate microemulsions S/Cos (2:1)

| Formulations | ME-1 | ME-2 | ME-3 | ME-4 | ME-5 | ME-6 | ME-7 | ME-8 | ME-9 |
|---|---|---|---|---|---|---|---|---|---|
| Drug (mg) | 250.75 | 250.75 | 250.75 | 250.75 | 250.75 | 250.75 | 250.75 | 250.75 | 250.75 |
| S/Cos (Smix) (g) | 10 | 11.25 | 11 | 10 | 10.5 | 9.5 | 8 | 7.75 | 6.25 |
| Oil (g) | 10 | 7.5 | 5.5 | 4 | 3.5 | 2.75 | 2 | 1.75 | 1.25 |
| Distilled Water (g) | 5 | 6.25 | 8.5 | 11 | 11 | 12.75 | 15 | 15.5 | 17.5 |
| Total weight (g) | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |

248.60 nm, with methanol serving as the blank. The oils, surfactants, and co-surfactants that exhibited the highest solubility for Brimonidine Tartrate were selectively included in the formulation of the microemulsions, ensuring optimal drug incorporation and stability in the final product.

*Construction of Pseudo Ternary Phase Diagrams*:

The methodology employed for the construction of pseudo ternary phase diagrams involved the water titration method, enabling a thorough depiction of the extent and characteristics of the microemulsion region. The surfactant and co-surfactant (Smix) were blended in distinct volume ratios (Km), specifically 1:1 and 2:1. To create each phase diagram, the ratio of oil to Smix was meticulously altered, ranging from 9:1 to 1:9 (w/w). In each oil: Smix mixture, water was systematically added drop-wise under magnetic stirring at ambient temperature, with continuous monitoring for alterations in appearance after each addition (Keng *et al.,* 2015).

The solution exhibited turbidity or cloudiness at the titration endpoint, signifying a crucial indication of microemulsion formation. The volume of water necessary to induce turbidity or cloudiness in the mixture was accurately recorded. Following this, the percentages of the components were precisely calculated and graphically represented on the pseudo-ternary phase diagram. This visual and quantitative represent-tation provided valuable insights into the phase behavior and composition of the microemulsion system. Pseudoternary diagrams were constructed using Ternaryplot.com, contributing to a comprehensive understanding of the intricate relationships among oil, surfactant, co-surfactant, and water within the microstructure of the formulation.

*Preparation of Brimonidine Tartrate Microemulsion*:

The formulation of the microemulsion containing Brimonidine tartrate was conducted using the phase titration method and constructing pseudo ternary phase diagrams of oil, surfactant/co-surfactants (S/Cos), and water mixtures. The fixed surfactant/co-surfactant weight ratio was maintained at 2:1 during the formulation processes (Andonova *et al.,* 2014).

In detail, pseudo ternary phase diagrams were generated, varying the concentrations of oil, water, surfactant, and co-surfactant for each case, while keeping the drug concentration constant as outlined in Table 1. A predetermined amount (10 mg/ml) of Brimonidine tartrate was accurately weighed and dissolved in the selected oil. Subsequently, surfactant and co-surfactant were added to the oily solution of the drug, and the

mixture was mechanically stirred using a magnetic stirrer to form an emulsion.Water was then added dropwise to the emulsion until the formation of a transparent mixture was achieved. The emergence of a transparent solution served as a crucial indicator of the successful formation of a microemulsion.

This formulation process ensured the consistent and precise development of Brimonidine tartrate microemulsions, setting the stage for subsequent evaluations and analyses.

*Evaluation of Brimonidine tartrate microemulsion*:

*Physical examination*:

The assessment of Brimonidine tartrate microemulsion involved a physical examination. After each incremental addition of water to the surfactant/co-surfactant (Smix) and oil mixture, a thorough visual inspection was conducted. The samples underwent scrutiny for characteristics such as emulsion, gel, or microemulsion formation based on visual observations.

*Determination of per cent drug content in microemulsion*:

The quantification of the drug content in the microemulsion formulation was carried out through a precise procedure. A volume of 1 ml from the microemulsion formulation was equivalent to 10 mg of the active drug and was carefully transferred into a 10 ml volumetric flask. Subsequently, the volume was adjusted by filling the flask with phosphate buffer. UV absorbance measurements were then conducted at a wavelength of 249.10 nm. This analytical approach enabled the determination of the percent drug content in the microemulsion formulation, providing valuable insights into the concentration of the active drug within the formulated product (Patel *et al.,* 2014).

*Determination of globule size in microemulsion*:

The evaluation of globule size distribution in the microemulsion formulations was conducted using the Malvern Particle Size Analyzer, a sophisticated instrument for precise measurements. For each formulation, 1 ml of the emulsion was carefully extracted and subsequently diluted to a total volume of 250 ml with distilled water. The diluted emulsion was then subjected to analysis using the Malvern Particle Size Analyzer, which provided accurate readings regarding the size distribution of the globules within the microemulsion. This analytical approach allowed for a comprehensive understanding of the particle sizes present in the formulations, contributing valuable information to the overall characterization and quality assessment of the microemulsion system.

*Preparation of microemulgel*:

To address the inherent low viscosity of microemulsions, which limits their application, a strategic approach involves incorporating them into gelling agents. The selected drug-loaded microemulsions, optimized for their performance, were chosen to formulate the Brimonidine tartrate microemulsion-based gel. The gelling agents employed in this formulation were Carbopol 934 and Carbopol 940, chosen based on insights from previous studies. To initiate the gel preparation process, 1% w/v of the gelling agents was soaked in water for a duration of 24 h, ensuring proper hydration. Subsequently, the pH of the Carbopol 934 and Carbopol 940 gel was adjusted to the range of 6-6.5 by the gradual addition of triethanolamine. The microemulsion-based gel was then prepared by amalgamating the optimized microemulsion with a distinct formulation of the gel base. The mixing was performed in a ratio of 1:1, and the entire process was executed with gentle stirring. This innovative approach effectively combines the advantages of microemulsions with the desirable characteristics of gels offering a versatile and effective solution for drug delivery with the potential for enhanced therapeutic outcomes (Charoenrein *et al.,* 2021).

*Evaluation of Microemulgel*:

*Physical Examination*

The assessment of the microemulsion-based gel involved a comprehensive visual examination. The formulation was meticulously scrutinized for its

appearance, colour, consistency, and homogeneity. This visual inspection played a crucial role in gauging the overall aesthetics and uniformity of the microemulgel, providing valuable insights into its potential for effective application and patient compliance.

*Measurement of pH*:

The determination of pH for various Microemulgel formulations was carried out utilizing a digital pH meter. In this process, 1 g of microemulgel was dissolved in 100 ml of distilled water. The pH measurements for each formulation were performed in triplicates, and the mean values were calculated. The triplicate measurements enhance the accuracy and reliability of the recorded pH values, contributing to a comprehensive understanding of the Micro-emulgel characteristics.

*Determination of drug content*:

Accurate quantification of drug content in the microemulgel formulation was conducted. Initially, 1 g of the microemulgel formulation was precisely weighed and dissolved in 100 ml of phosphate buffer. Subsequently, the solution underwent sonication for duration of 2 h to facilitate optimal dissolution. Post-sonication, the solution was subjected to filtration through filter paper, and the filtrate's absorbance was measured spectrophotometrically at 249.10 nm. The concentration of Brimonidine tartrate in mg/ml was determined by referencing the standard calibration curve of the drug. This comprehensive approach to drug content determination was performed in triplicate for each formulation batch, ensuring robust and reliable results. Mean values were calculated, contributing to a thorough understanding of the drug concentration within the microemulgel formulations (Singla *et al.,* 2013).

*Spreadability evaluation*:

The assessment of spreadability for the emulgel formulations involved a methodical experiment to gauge the uniformity and ease of spreading. To initiate the process, an additional 2 g of emulgel was evenly spread on a glass slide. The emulgel formulation was then positioned between the first and second glass slides, matching the diameter of the fixed first slide. The second glass slide was affixed to a hook, and a 1 kg weight was applied to the top of the two slides for 5 min. This step aimed to eliminate air and establish a consistent film of the emulgel between the slides.

Subsequently, an ample quantity of weight bars was strategically positioned in the pan attached to the pulley using a hook. On the side where the weight was applied, the time in seconds required for the upper slide to move a certain distance and separate from the lower slide was diligently noted. This entire experiment was conducted in triplicate, and the mean of these determinations was calculated for each formulation (Basera *et al.*, 2015).

Spreadability (S) was quantitatively determined using the following formula:

$$S= M \times L/T$$

Where, S = Spreadability (g.cm/sec); M = Weight tied to upper slide (g); L = Length of glass slides (cm); and T = Time taken to separate the slides from each other (Sec).

*Rheological study*:

The exploration of the rheological properties of the microemulsion-based gel was conducted to understand its viscosity characteristics. Using a Brookfield Viscometer, the measurement was performed by immersing spindle number 62 in the microemulsion and rotating it at 50 rpm under ambient temperature conditions. The viscosity, expressed in centipoises (cps), was carefully determined (Kaushik *et al.*, 2013).

This rheological study provided valuable insights into the flow and deformation behaviour of the microemulsion-based gel, contributing to a comprehensive understanding of its physical properties and suitability for specific applications.

*In vitro drug release study*:

The investigation into the *in vitro* drug release

profile of the microemulgel was systematically conducted using a modified Franz Diffusion cell equipped with a dialysis membrane. The membrane, pre-soaked in a phosphate buffer of pH 7.4 for 9-12 h, was delicately clamped between the donor and receptor compartments.

1 g of the drug-loaded microemulsion-based gel, equivalent to 10 mg of Brimonidine tartrate, was placed in contact with the dialysis membrane within the donor compartment. Subsequently, 50 ml of phosphate buffer at pH 7.4, employed as the dissolution media, was added to the receptor compartment. The donor compartment remained in contact with the receptor compartment throughout the study (Udmale *et al.*, 2019).

This assembly was positioned on a magnetic stirrer, ensuring continuous stirring of the solution on the receptor side using a magnetic bead. The temperature of the cell was diligently maintained at 37 ± 0.5°C to simulate physiological conditions. At specified time intervals, 1 ml samples were withdrawn and replaced with an equal volume of fresh dissolution media (Rajput *et al.*, 2013). The collected samples were analyzed spectrophotometrically at 249.10 nm, and the cumulative percentage of drug release was calculated. The resulting data were used to generate a graph plotting the percentage of cumulative drug release against time, providing a comprehensive depiction of the microemulgel's drug release kinetics.

*Stability studies*:

A short-term stability assessment was conducted on the optimized formulation to evaluate its robustness under various storage conditions. The formulation underwent exposure to different temperatures and relative humidity levels, specifically at 25°C ± 2°C / 60% ± 5% RH and 40°C ± 2°C / 75% ± 5% RH, over a duration of 1 month.

At regular intervals of 15 days, samples were withdrawn from the stability chambers, and a comprehensive evaluation was performed, focusing on both rheological properties and drug content. This systematic examination aimed to assess the formulation's stability and integrity over time under diverse environmental conditions, providing valuable insights into its shelf-life and performance characteristics (Ashara *et al.*, 2014).

## Results and Discussion

*Preformulation studies*

- *UV spectroscopic study*

(a) *Determination of wavelength using UV spectroscopic study*

The absorption maxima of Brimonidine tartrate in methanol and phosphate buffer (pH 7.4) were found to be 248.60 nm and 249.10 nm, respectively, which matched the reported wavelength and mentioned in Figures 1 and 2.

(b) *Preparation of calibration curve*

The calibration curves of Brimonidine tartrate in methanol and phosphate buffer (pH 7.4) were prepared and shown in Tables 2, 3 and Figures 3, 4, respectively.

- *Drug Characterization*

(a) *Melting point determination*:

The melting point of BT was found to be 207-208$^0$C, which was found to be the same as reported in the literature, and Table 4 shows the melting point of BT.

(b) *Determination of solubility of Brimonidine tartrate*:

The solubility of Brimonidine Tartrate in methanol and phosphate buffer (pH 7.4) was studied, and the result of the study is shown in Table 5.

(c) *Drug- Excipient interaction study*:

TLC analysis discovered that there was no interaction between the Brimonidine tartrate and excipients. In the present investigation, it was found that there were no chemical and physical interactions between the drug and excipients. Hence it was proven that the drug was authentic and free from impurities and the results are shown in Table 6.

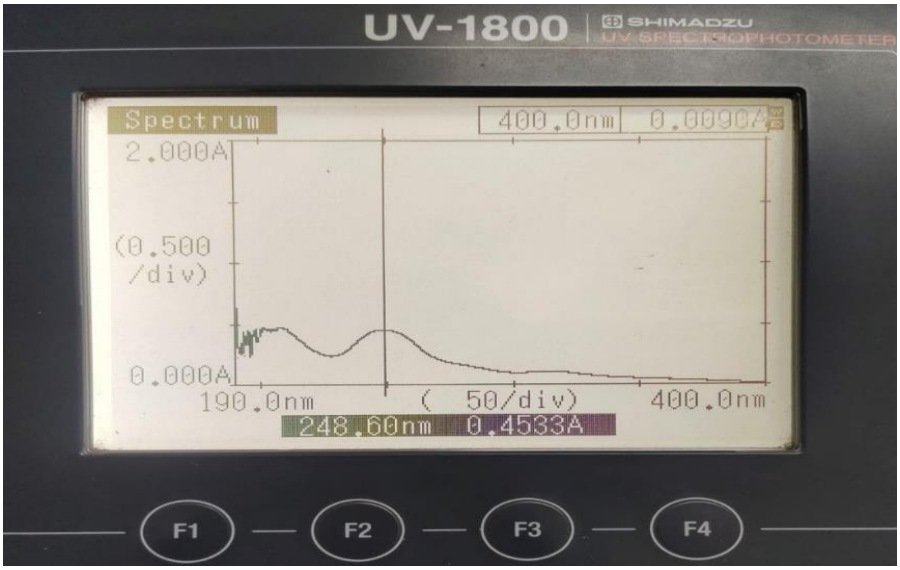


Fig. 1: UV spectrum of BT in methanol.

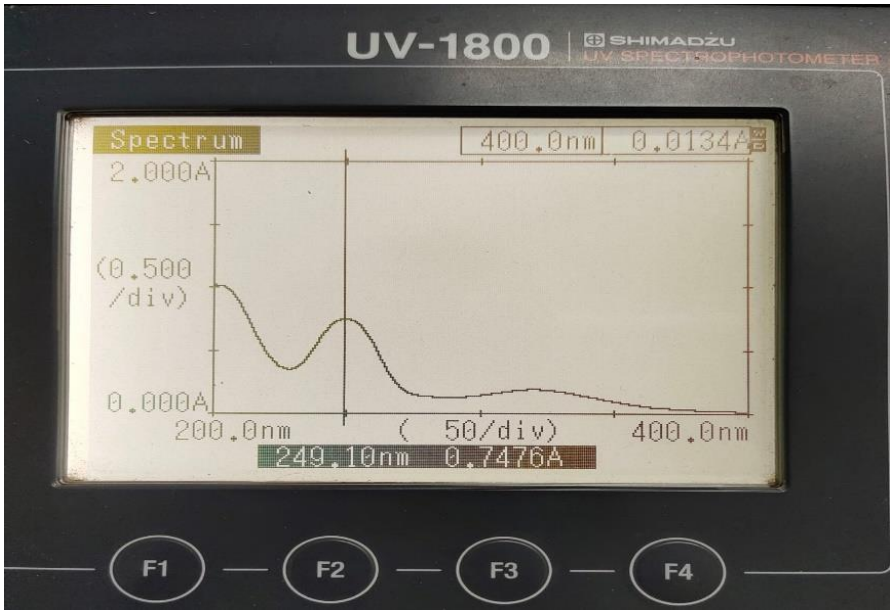


Fig. 2: UV spectrum of BT in phosphate buffer 7.4.

Table 2: Absorbance data of BT in methanol

| S. No. | Concentration (µg/ml) | Absorbance (n=3) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.0873±0.0012 |
| 3 | 4 | 0.1903±0.0020 |
| 4 | 6 | 0.2830±0.0052 |
| 5 | 8 | 0.3907±0.034 |
| 6 | 10 | 0.4665±0.0036 |

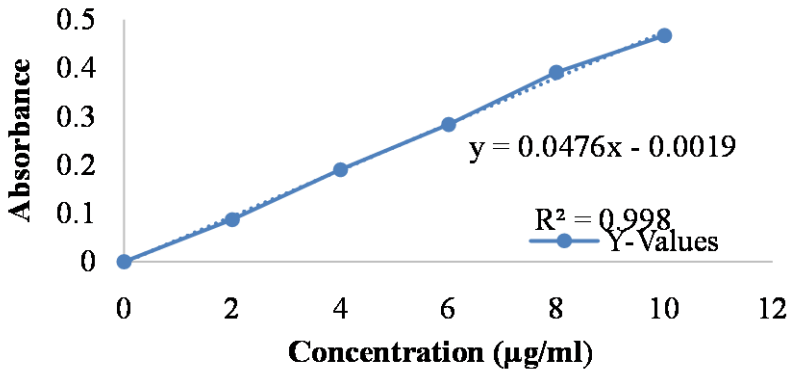


Fig. 3: Calibration curve of BT in Methanol at 248.60 nm.

Table 3: Absorbance data of BT in phosphate buffer 7.4

| S. No. | Concentration (µg/ml) | Absorbance (n=3) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.1585±0.0023 |
| 3 | 4 | 0.3081±0.0057 |
| 4 | 6 | 0.4682±0.0032 |
| 5 | 8 | 0.5965±0.015 |
| 6 | 10 | 0.7319±0.0092 |

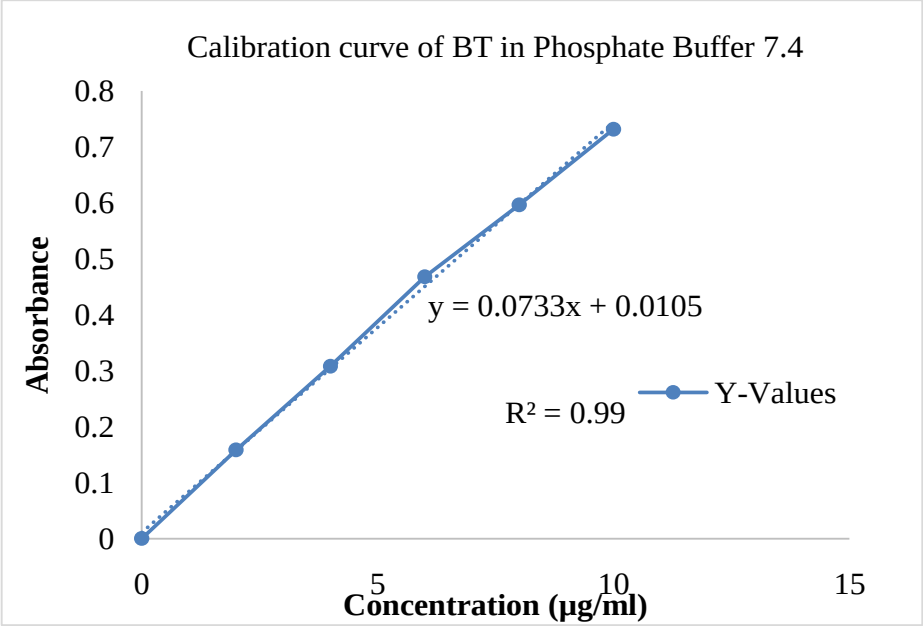


Fig. 4: Calibration curve of BT in phosphate buffer 7.4 at 249.10.

Table 4: Melting point of BT

| S. No. | Melting Point of Standard drug (°C) | Melting Point of Sample drug (°C) | Average melting point of the sample (n=3) (°C) |
|---|---|---|---|
| 1 | 207-209 | 207-209 | 207-208 |
| 2 | | 207-208 | |
| 3 | | 207-209 | |

Table 5: Solubility data of BT in different mediums

| Name of Drug | Medium (n=3) | |
|---|---|---|
| | Methanol (mg/ml) | Phosphate buffer (pH 7.4) (mg/ml) |
| Brimonidine Tartrate | 1.6 ±0.53 | 1.14 ±0.26 |

Table 6: Data of drug-excipient interaction study

| S. No. | Drug/drug + Excipient Ratio (1:1) | Initial day (Rf) | After 14 days (Rf) | Inference |
|---|---|---|---|---|
| 1 | Drug (Brimonidine Tartrate) | 0.52 | 0.52 | No change |
| 2 | Drug + Tween 80 | 0.56 | 0.56 | No change |
| 3 | Drug + Propylene glycol | 0.62 | 0.62 | No change |
| 4 | Drug + Orange oil | 0.64 | 0.63 | No change |
| 5 | Drug + Carbopol 934 | 0.54 | 0.55 | No change |
| 6 | Drug + Carbopol 940 | 0.56 | 0.56 | No change |

*Formulation and development of microemulgel*

(1) *Screening of formulation components by solubility studies*:

(a) *Screening of excipients based on solubility*:

For the preparation of microemulsion, the solubility of Brimonidine tartrate in different oils, surfactants, and co-surfactants was screened, and the results are shown in Tables 7, 8, 9 and Figures 5, 6, 7.

The solubility of Brimonidine Tartrate in Orange oil was found to be 10.22 ± 0.56 mg/ml, the highest among the oils investigated. Amongst the various surfactant and co-surfactant screened, Brimonidine tartrate was found to have good solubility in Tween 80 (4.29±0.06) surfactant, whereas the Propylene Glycol (2.159±0.013) exhibited superior solubility amongst the co-surfactant screened in preliminary studies.

(b) *Screening of the selected surfactant and co-surfactant for its emulsification ability*:

The o/w microemulsion region was identified in the pseudo-ternary phase diagram. A high concentration of oil and surfactant in the formulation can cause toxicity and skin irritation. It should be determined properly, and an optimum concentration should be used. The maximum safe concentration of Smix was selected as 60%. The pseudo-ternary phase diagrams of Orange oil with Tween 80 and Propylene glycol at various Km ratios, i.e. 1:1 and 2:1, are represented in Figure 8. The microemulsion area is represented by the coloured portion in the phase diagram, while the non-coloured portion represents the existence of a turbid and conventional emulsion. The phase diagram with the $S_{mix}$ ratio of 2:1 showed the

Table 7: Solubility data of BT in different oils

| S. No. | Oils | Solubility in mg/ml (n=3) |
|---|---|---|
| 1 | Orange Oil | 10.22 ± 0.56 |
| 2 | Light Liquid Paraffin | 1.55±0.06 |
| 3 | Sesame oil | 0.83±0.04 |
| 4 | Sunflower oil | 0.075±0.0002 |
| 5 | Soyabean oil | 0.0083±0.0004 |
| 6 | Isopropyl myristate | 0.0053±0.0005 |

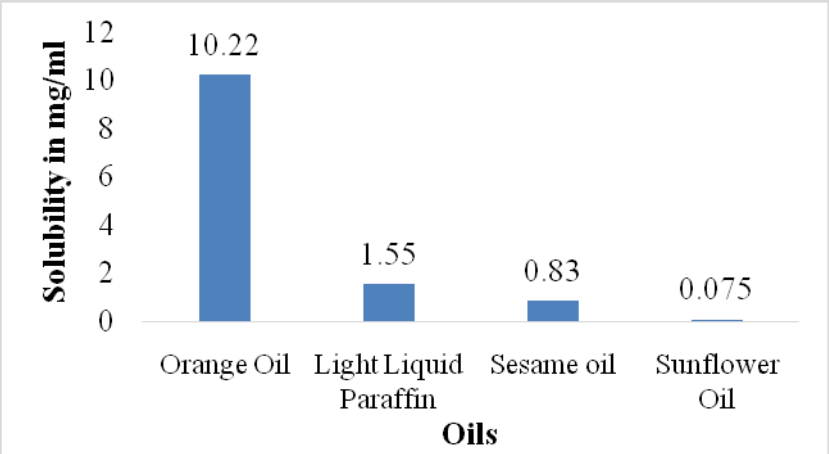


Fig. 5: Solubility profile of BT in different oils.

Table 8: Solubility data of BT in different surfactants

| S. No. | Surfactants | Solubility in mg/ml (n=3) |
|---|---|---|
| 1 | Tween 80 | 4.29±0.06 |
| 2 | Tween 20 | 1.79±0.04 |

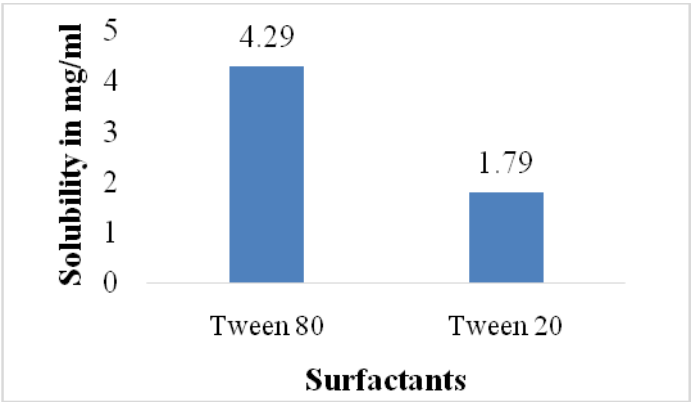


Fig. 6: Solubility profile of BT in different surfactants.

Table 9: Solubility data of BT in different co-surfactants

| S. No. | Co-surfactants | Solubility in mg/ml (n=3) |
|---|---|---|
| 1 | Propylene Glycol | 2.159±0.0013 |
| 2 | Span 80 | 0.7186±0.03 |
| 3 | Span 20 | 0.134±0.02 |
| 4 | PEG 400 | 1.325±0.5 |

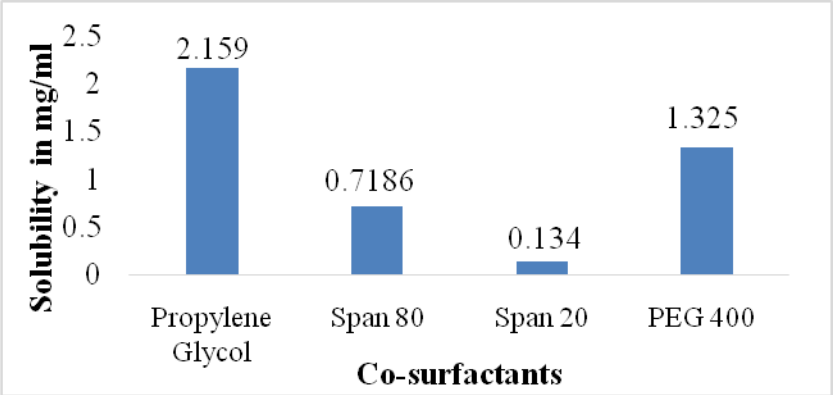


Fig. 7: Solubility profile of BT in different Co-surfactant.

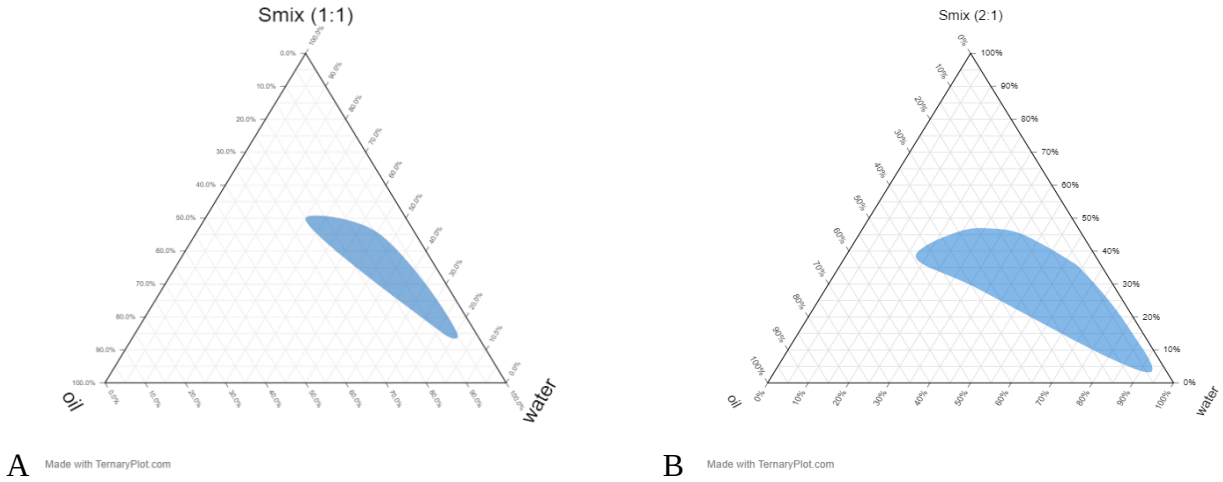


Fig. 8: Pseudo-ternary phase diagrams of MEs comprising Orange oil, Smix (Tween 80: Propylene glycol), and water at various oil: Smix ratios; (A) 1:1, (B) 2:1.

highest area of emulsification and was therefore selected for further studies. It can be seen that an increase in the weight ratio of Tween 80 and Propylene glycol resulted in an expansion of the microemulsion region. This may be due to the reduction of the interfacial tension, increasing the fluidity of the interface and thereby increasing the entropy of the system.

➢ *Evaluation of the microemulsions*

(a) *Physical examination*:

The samples were identified as microemulsions when they appeared translucent/transparent.The sample was identified as emulsions when they

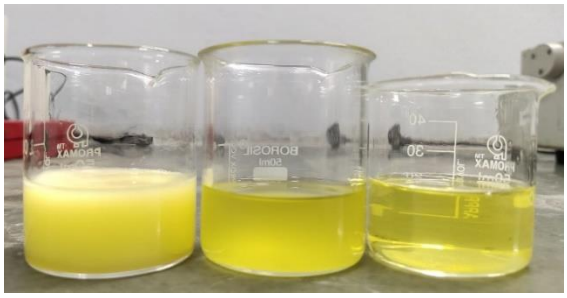

Fig. 9: Difference between emulsion and microemulsion formulations.

Table 10: Drug content of BT

| Formulations | Drug content (%) |
|---|---|
| ME-6 | 95.31±0.25 |
| ME-7 | 97.15±0.08 |
| ME-8 | 99.53±0.26 |
| ME-9 | 98.84±0.59 |
| Maximum | 99.53 |
| Minimum | 95.31 |
| Average | 97.70 |

appeared as turbid or milky liquids. In Figure 9, the first formulation was found to be turbid and milky, so it considered emulsions with two-phase. The second and third formulation was transparent/translucent liquid, so they considered microemulsion with only one phase. Formulation ME-1 to ME-5 was milky, white in appearance, considered emulsions, and rejected.

(b) *Determination of per cent drug content*:

The percentage of the drug content of all the formulations varied from 95.31% to 99.53%, as shown in Table 10. This result indicates that there was a uniform distribution of the drug throughout the batch.

(c) Globule *size determination*:

The concentration of the oil phase in the formulated microemulsion affected the globule size. The average globule size increased with the increase in the concentration of the oil. The smaller globule size of the microemulsion was obtained due to the higher concentration of surfactant and cosurfactant in the microemulsion system. The decrease in the globule size can be attributed to the solubilization of the internal phase within a larger number of surfactant micelles, which are consequently swollen to a lesser extent. The particle size of the micro-emulsion was shown in Figures 10, 11, 12, 13, and Table 11.

➢ *Evaluation of Microemulgel*

(a) *Physical examination*:

All the prepared formulations were yellow and transparent in appearance and showed good homogeneity and consistency. The results are shown in Table 11.

(b) *Measurement of pH*:

The pH of all the formulations was found to be ranging from 5.73 to 6.44, which was found to be acceptable to avoid any skin irritation. The results are shown in Table 12.

(c) *Determination of spreadability*:

Spreadability is the term expressed to denote the extent of the area to which the emulgel spreads on application to the skin or affected part. The

Table 11: Globule size of BT microemulsion

| Formulations | Particle size (nm) |
|---|---|
| ME-6 | 847 |
| ME-7 | 348.8 |
| ME-8 | 240.6 |
| ME-9 | 224.6 |

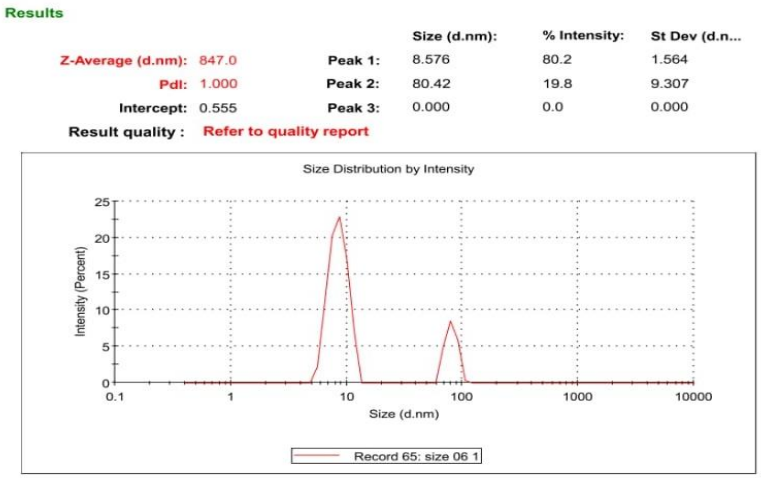


Fig. 10: Particle size of the ME 6.

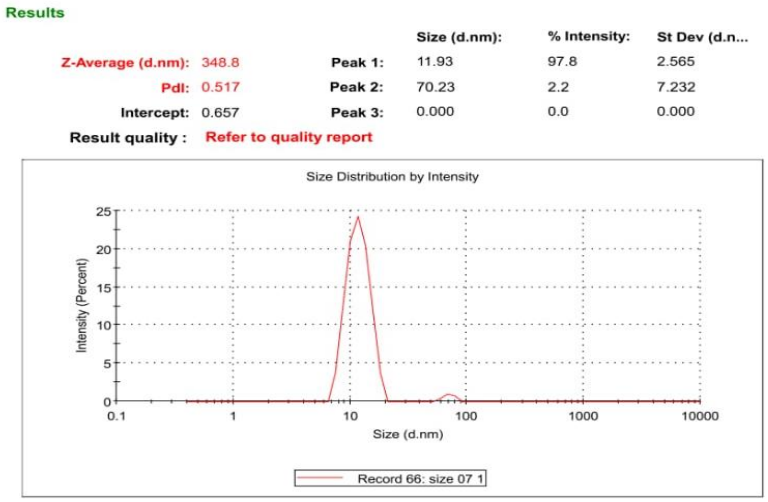


Fig. 11: Particle size of the ME 7.

therapeutic efficacy of formulation depends upon its spreading value. The Spreadability value ranged from 28.73 to 36.45 g cm/sec, as shown in Table 12.

(d) *Determination of per cent drug content*:

The percentage drug content of prepared emulgel was found in the range of 94.40 to 98.36%. The results are shown in Table 13. The highest drug content, i.e. 98.36%, was obtained for the formulation MEG-7 of emulsion and gelling agent in the concentration of 1% Carbopol 940.

(e) *Rheological study*:

The viscosities of different emulgel formulations are shown in Table 13. The viscosity ranged

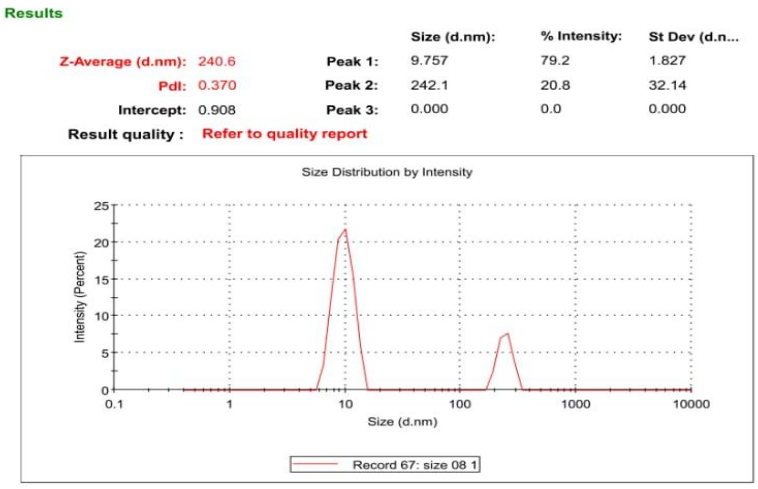


Fig. 12: Particle size of the ME 8.

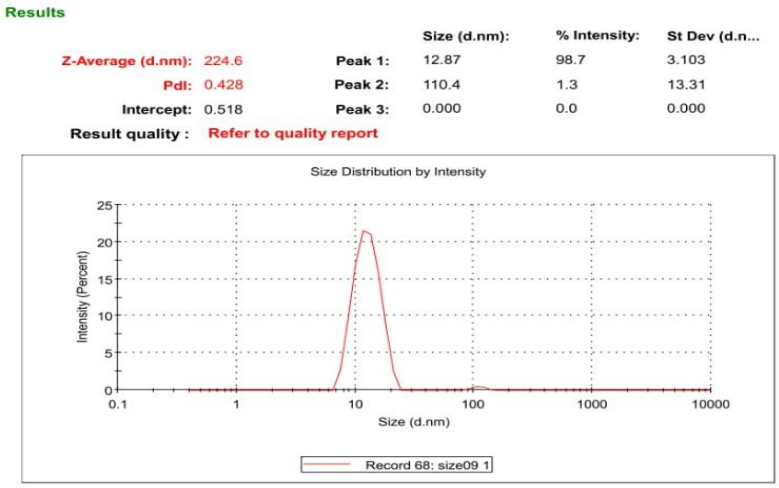


Fig. 13: Particle size of the ME 9.

Table 12: Appearance, drug content, pH of prepared microemulgel

| S. No. | Formulation Code | Appearance | pH | Spreadability (g. cm/sec) |
|---|---|---|---|---|
| 1 | MEG-1 (Carbopol 934 1%) | Yellow Transparent | 5.95 ±0.40 | 36.45 ±2.62 |
| 2 | MEG-2 (Carbopol 934 1%) | Yellow Transparent | 5.82 ±0.06 | 35.72 ±0.94 |
| 3 | MEG-3 (Carbopol 934 1%) | Yellow Transparent | 6.44 ±0.45 | 35.11 ±1.24 |
| 4 | MEG-4 (Carbopol 934 1%) | Yellow Transparent | 5.73 ±0.12 | 33.98 ±0.81 |
| 5 | MEG-5 (Carbopol 940 1%) | Yellow Transparent | 5.97 ±0.51 | 31.12 ±0.52 |
| 6 | MEG-6 (Carbopol 940 1%) | Yellow Transparent | 6.03 ±0.35 | 29.88 ±1.35 |
| 7 | MEG-7 (Carbopol 940 1%) | Yellow Transparent | 5.93 ±0.54 | 30.73 ±0.96 |
| 8 | MEG-8 (Carbopol 940 1%) | Yellow Transparent | 5.98 ±0.18 | 32.18 ±0.45 |

Table 13: Viscosity, per cent drug content of prepared microemulgel

| S. No. | Formulation Code | Viscosity (cps) | Drug Content (%) |
|---|---|---|---|
| 1 | MEG-1 (Carbopol 934 1%) | 2325 ±255.44 | 94.40±0.28 |
| 2 | MEG-2 (Carbopol 934 1%) | 3970 ±425.85 | 95.95±0.39 |
| 3 | MEG-3 (Carbopol 934 1%) | 4058 ±362.52 | 98.23±0.42 |
| 4 | MEG-4 (Carbopol 934 1%) | 4265 ±360.25 | 97.61±0.09 |
| 5 | MEG-1 (Carbopol 940 1%) | 5625 ±254.12 | 94.53±0.35 |
| 6 | MEG-2 (Carbopol 940 1%) | 6520 ±235.36 | 96.15±0.06 |
| 7 | MEG-3 (Carbopol 940 1%) | 5850 ±302.42 | 98.36±0.15 |
| 8 | MEG-4 (Carbopol 940 1%) | 6350 ±112.56 | 97.10±0.11 |

Table 14: *In vitro* % drug release of MEG-1 to MEG-4 formulations (n=3)

| Time (h) | MEG-1 | MEG-2 | MEG-3 | MEG-4 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 15.8 ±0.32 | 16.6 ±0.43 | 16.9 ±1.24 | 16.8 ±0.64 |
| 2 | 24.8 ±1.24 | 25.6 ±0.53 | 29.6 ±0.48 | 27.4 ±1.13 |
| 3 | 33.9 ±1.45 | 39.1 ±0.57 | 44.7 ±1.23 | 40.6 ±0.54 |
| 4 | 43.9 ±0.93 | 52.4 ±1.45 | 57.3 ±1.25 | 56.2 ±0.25 |
| 5 | 58.1 ±1.02 | 62.2 ±0.89 | 67.4 ±0.53 | 66.6 ±1.53 |
| 6 | 64.1 ±0.89 | 73.1 ±1.86 | 76.5 ±1.64 | 75.5 ±0.86 |
| 7 | 74.0 ±0.57 | 86.1 ±0.25 | 91.7 ±1.56 | 88.8 ±0.95 |

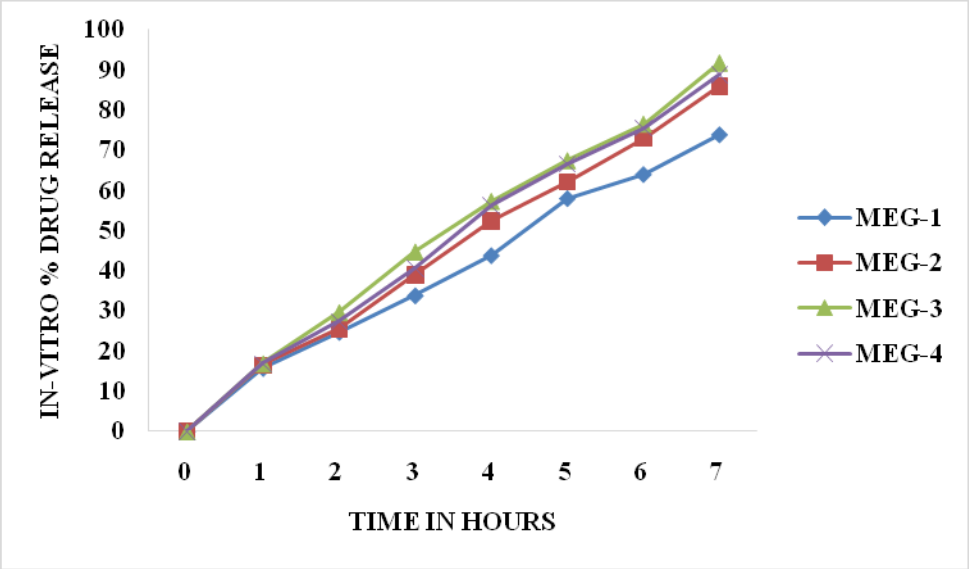


Fig. 14: *In vitro* % drug release of MEG-1 to MEG-4 formulations.

Table 15: *In vitro* % drug release of MEG-4 to MEG-8 formulations (n=3)

| Time (h) | MEG-5 | MEG-6 | MEG-7 | MEG-8 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 1 | 13.56 ±0.65 | 14.5 ±0.53 | 16.6 ±1.46 | 15.87 ±0.84 |
| 2 | 25.9 ±1.35 | 28.9 ±1.67 | 32.9 ±0.95 | 25.6 ±1.75 |
| 3 | 35.4 ±0.75 | 37.7 ±0.87 | 44.1 ±0.48 | 37.6 ±0.94 |
| 4 | 48.3 ±0.83 | 47.9 ±1.05 | 56.9 ±1.94 | 49.28 ±1.74 |
| 5 | 55.5 ±1.42 | 56.7 ±0.84 | 66.5 ±1.92 | 58.88 ±1.02 |
| 6 | 64.3 ±1.86 | 66.9 ±1.75 | 73.6 ±1.62 | 67.19 ±0.82 |
| 7 | 73.6 ±0.89 | 75.7 ±1.23 | 84.8 ±0.96 | 79.79 ±1.45 |

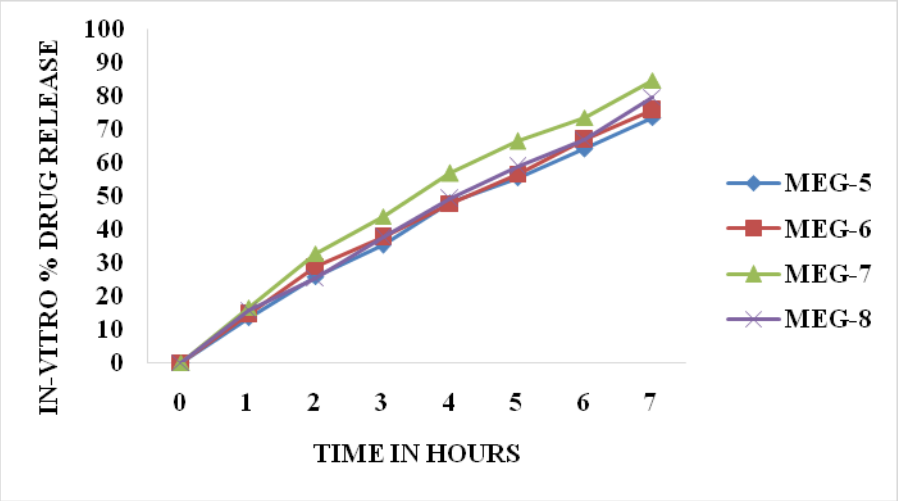


Fig. 15: *In vitro* % drug release of MEG-5 to MEG-8 formulations.

Table 16: Stability study of microemulgel at the Accelerated condition

| S. No. | Parameter | Stored at 40°C ± 2°C and 75%±5% RH | | |
|---|---|---|---|---|
| | | Initial day | 15 days | 30 days |
| 1 | Drug content (%) | 98.23 ±0.65 | 98.01 ±0.98 | 98.01 ±0.95 |
| 2 | pH | 6.43 ±1.4 | 6.41 ±0.16 | 6.41 ±0.16 |
| 3 | Viscosity(cps) | 4058 ±362 | 4062 ±401 | 4061 ±360 |
| 4 | Appearance | Yellow Transparent | Yellow Transparent | Yellow Transparent |

between 2325 to 6520 cps. The results showed that the emulgel formulations prepared by using carbopol 940 showed higher viscosity as compared to that of carbopol 934.

(f) *In vitro* per cent drug release study:

All formulations showed % drug release within a range of 73.6% to 91.7% after 7 h. The maximum release was observed in the case of MEG-3 formulation i.e.,91.7%. The *in vitro* % drug release data is shown in Tables 14, 15, and Figures 14, 15.

Table 17: Stability study of microemulgel at Room Temperature

| S. No. | Parameter | Stored at 25°C ± 2°C and 60%±5% RH | | |
|---|---|---|---|---|
| | | Initial day | 15 days | 30 days |
| 1 | Drug content (%) | 98.23 ±0.98 | 98.23 ±0.95 | 98.01 ±0.65 |
| 2 | pH | 6.43 ±1.4 | 6.43 ±1.5 | 6.43 ±0.9 |
| 3 | Viscosity(cps) | 4058 ±362 | 4058 ±301 | 4055 ±360 |
| 4 | Appearance | Yellow Transparent | Yellow Transparent | Yellow Transparent |

(g) *Stability studies*:

MEG-3 optimized formulation was examined for up to 1 month for any appearance, change in pH, viscosity, and % drug content as shown in Tables 16, 17.

The stability study reveals that the optimized formulation of microemulgel MEG-3 shows less deviation, so it can be concluded that it showed acceptable stability at a given temperature and humidity.

## Conclusion

Brimonidine tartrate is a selective α2 –adrenergic receptor agonist and is the first topical treatment approved for facial erythema of rosacea. Brimonidine tartrate belongs to BCS class-II drug. A literature survey shows Brimonidine tartrate peaks benefit between 3 and 6 h after application. Formulating a topical microemulgel of Brimonidine tartrate may improve bioavailability and efficacy by enhancing penetrability and solubility. In the primary stage, we studied and worked on the literature reviews of various research and review articles regarding microemulgel and rosacea. After that, we studied various excipients to be used in the formulation. After selecting the excipient, a preformulation study was performed in which drug identification, solubility, and drug excipients interaction or compatibility studies were performed. Afterward, screening of components such as oil, surfactant, co-surfactant, and Smix ratio could be done. The selection of oil, surfactant, and co-surfactant was selected based on solubility. The water titration method was used to determine the Smix ratio. A pseudo-ternary diagram was used to select the concentration of components using ternaryplot.com. Then, orange oil consumed the maximum amount of Brimonidine tartrate and is thus chosen as a vehicle for the microemulsion oil phase. Tween-80 and propylene glycol at appropriate ratios were selected as ideal surfactants and co-surfactant. Based on the Physical Inspection, Drug Content, and Globular Size, ME-6 to ME-9 were selected. From all the formulated batches ME-8 was found best formulation, the particle size of the best formulation was found to be 240.6 nm and the drug content of the best formulation (ME-8) was found to be 99.53%. The microemulsions were then incorporated into a 1% Carbopol 934 and 1% Carbopol 940 gel base. Triethanolamine was used as a pH adjustment. The developed formulations were later on evaluated. All the formulation batches (MEG-1 to MEG-8) were evaluated for physical examination, measurement of pH, determination of % drug content, determination of spreadability, rheological study, *in vitro* % drug release study, and stability studies. So, considering all 8 formulations, formulation MEG-3 was found to be an optimized formulation from the data obtained.The formulation MEG-3 shows a maximum release of up to 91.7% within 7 h. Stability study performed by storing at ICH storage condition for 30 days. There was no significant change in % drug content, viscosity, pH, and physical appearance at long-term conditions (25 ±2° C and 60 ±5% RH) but the formulation in accelerated conditions (40 ± 2°C and 75±5% RH)

show minor fluctuation in % drug content, viscosity, pH but no change in the physical appearance. The prepared microemulgel of Brimonidine tartrate overcomes the problem of poor solubility, poor absorption, and poor bioavailability.

## Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

## Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. They collaborated in designing the research, conducting thorough analysis, drafting the manuscript, and refining its content. Their collective efforts ensured a well-structured and high-quality study, reflecting their shared commitment to its successful completion. All authors have read and agreed to the published version of the manuscript.

## Conflict of Interest

The authors declare no conflicts of interest.

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