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CHARACTERIZATION OF MICONAZOLE NITRATE LOADED TOPICAL MICROEMULSION GEL USING CARICA PAPAYA SEED OIL AND CINNAMON OIL

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ABSTRACT

The present study aimed to develop and evaluate Miconazole nitrate microemulsions incorporating Carica papaya seed oil and Cinnamon oil to enhance antifungal activity. Microemulsions were prepared by titrating various ratios of oil to Smix with water, and the microemulsion region was identified using pseudo-ternary phase diagrams. The formulations were characterized for compatibility, transmittance, viscosity, pH, drug content, globule size, zeta potential, and stability. FTIR studies confirmed no significant interaction between the drug and excipients. Among all, CPM3 and CCM3 were selected as optimized formulations due to their high transmittance, low viscosity, high drug content, and ideal pH suitable for topical application. These optimized microemulsions were incorporated into 1% Carbopol 934 gel to form CPM3-G1 and CCM3-G2 gels. The prepared gels exhibited good spreadability, appropriate viscosity, and sustained drug release profiles. In vitro studies confirmed prolonged drug release. The study concluded that the combination of Miconazole nitrate with Carica papaya seed oil and Cinnamon oil in microemulsion form significantly improves topical drug delivery and provides better therapeutic efficacy.

KEYWORDS: Microemulsion, Pseudoternary phase diagram, Miconazole nitrate, Carica papaya seed, Cinnamon oil, Anti-fungal agent.

INTRODUCTION[1-7]

Topical drug delivery system: Drugs known as topical preparations are applied topically to specific body parts. Formulations that solely impact a specific area of the body and are designed to minimize systemic absorption of the drug are referred to by this term. The conventional topical drug delivery techniques basically involve either breaking down the horny layer at the molecular level or assisting or manipulating the skin's barrier function (topical antibiotics, anti-bacterial, emollients, and sunscreen agents) in order to deliver drugs to the viable epidermal and dermal tissues without the use of oral, systemic, or other therapies.

A microemulsion is a good candidate for oral delivery of poorly water-soluble drugs because of its ability to improve drug solubilization. Absorption rate of a drug increases as its thermodynamic activity in the vehicle increases.

Microemulsions are widely used for topical drug delivery, which are optically isotropic and thermodynamically stable systems of water, oil, surfactant, and/or co-surfactant have been investigated as drug delivery systems due to their ability to solubilize poorly water-soluble drugs and to improve topical and systemic availability. It has quick and effective skin penetration and aids in the solubilization of the lipophilic drug moiety.

As a result, it is beneficial when administering topical medications. Transparent, isotropic, and thermodynamically stable mixtures of two immiscible liquids, microemulsions are made possible by the presence of a suitable surfactant, usually in conjunction with a cosurfactant. In addition to the usual advantages of improved drug stability and availability as a result of surfactant solubilization, the microemulsion method significantly affects transdermal dispersion. Additionally, because microemulsion sizes are usually quite small, they are a great way to deliver drugs. Microemulsion hence has great potential for drug delivery through the skin.

Miconazole nitrate, a synthetic imidazole derivative, has a wide range of antibacterial action and can be used to treat fungal infections both locally and systemically. In particular, it is effective against species of Microsporum, Trichophyton, Epidermophyton, and Candida. having some ability to combat gram-positive bacteria. It indicates that the cell membrane is the main site of action. According to research using Candida albicans, miconazole selectively inhibits the uptake of mucopolysaccharides (glutamine) and RNA and DNA precursors

(purines) at low concentrations by acting mainly on the yeast cell membrane.

Therefore, the goal of the current study is to investigate the antifungal effect of Miconazole Nitrate in combination with essential oils such as Carica papaya seed oil and cinnamon oil to create a microemulsion gel and examine the advantages of a stronger antifungal effect.

MATERIALS AND METHODS[8,9]

Materials

The following chemicals and reagents were used in the study. Miconazole Nitrate (Pharma grade, Mahrshee Laboratories, Gujarat*)* served as the active antifungal drug**.** Carica papaya seed oil and Cinnamon oil (LR grade, RV Essential, New Delhi) were used as natural antifungal agents with synergistic activity. Tween 20 and Tween 80 (LR grade, Thomas Baker Pvt. Ltd., Mumbai*)* acted as non-ionic surfactants for microemulsion stabilization**.** Propylene glycol and PEG 400 (LR grade, S D Fine Chem Ltd., Mumbai*)* were used as co-surfactants and penetration enhancers**.** Carbopol 934 (LR grade, CDH Pvt. Ltd., New Delhi*)* served as a gelling agent for microemulsion gel formation. Methanol (LR grade, S D Fine Chem Ltd., Mumbai) was used as a solvent. Potassium dihydrogen orthophosphate (Thermo Fisher Scientific, Mumbai) and Sodium hydroxide (S D Fine Chem Ltd., Mumbai) were used for buffer preparation and pH adjustment. All chemicals were of analytical or laboratory reagent grade and used without further purification.

Method of preparation of Microemulsion gel

The drug was first dissolved in the selected oil, followed by the addition of a fixed ratio of surfactant and co-surfactant. The resulting mixture was vortexed continuously for about 15 minutes to ensure proper mixing. Subsequently, the required quantity of demineralized water was added dropwise to the mixture with constant stirring. The process was continued until a clear and transparent liquid was obtained, indicating the formation of a microemulsion. The prepared microemulsion was then incorporated into a 1% w/w Carbopol 934 gel base to obtain the final microemulsion gel formulation suitable for topical application.

Formulation development based on Pseudoternary phase

Formulation Code	Smix ratios	Co- surfactant	Surfactant	Oils	Percent w/w component in formulation			
					Oil %	Smix %	Water %	Drug %
CPM1	1:1	Propyleneglycol	Tween 80	Carica papaya seed oil	16	64	20	1
CPM2	2:1				30	54	15	1
CPM3	3:1				37	50	13	1
CCM1	1:1			Cinnamon oil	26	55	17	1
CCM2	2:1				25	54	22	1
CCM3	3:1				32	50	18	1

EVALUATION OF MICROEMULSION[10-15]

Percent transmittance: The transparency of the microemulsion was determined by measuring the percentage transmittance at 272nm against distilled water as blank by using UV spectrophotometer.

%T= Antilog (2-Absorbance)

Viscosity measurements: The Rheological behaviour of the microemulsion formulation was evaluated using an Ostwald viscometer at a room temperature**.**

Measurement of pH: The pH of Miconazole nitrate microemulsion formulations was determined by using digital pH meter The measurement of pH of each formulation was done in triplicate and average values were calculated.

% Drug content: For the determination of drug content about one ml of each microemulsion formulation was transfer to a 10 ml volumetric flask and dissolved in methanol. It was diluted appropriately and analyzed spectrophotometrically at 272 nm.

Measurement of globule size and zeta potential: The average globule size and zeta potential of the optimized microemulsions were measured using a Malvern Zeta seizer instrument at a temperature 25 °C.

Surface morphology: Surface morphology of the optimized microemulsion formulations CPM3 and CCM3 will be determined by using a scanning electron microscope (SEM).

***In- vitro* diffusion study:** In *In vitro* diffusion study, the diffusion medium used was phosphate buffer pH 6.8. Assembly of diffusion cell for *In vitro* diffusion studies the diffusion cell was designed as per the dimension given. Diffusion cell with an effective diffusion area of 3.14 cm^2 was used for *In vitro* permeation studies. The egg membrane was mounted on the cell carefully so as to avoid the entrapment of air bubble under the egg membrane. Intimate contact of egg membrane was ensured with receptor fluid by placing it tightly with clamp. The diffusion cells were placed on the receptor compartment with magnetic stirrer. Then add 1gm of microemulsion to the donor compartment and 200ml of phosphate buffer pH 7.4 to receptor compartment. The speed of the stirrer and temperature was kept constant throughout the experiment. With the help of 1ml pipette 1 ml of sample was withdrawn at a time interval of 60 min (0 to 6hrs) from receptor compartment and same volume was replaced with receptor medium in order to maintain sink condition. The samples were appropriately diluted and the absorbance was measured at 272 nm using UV spectrophotometer.

EVALUATION OF MICONAZOLE NITRATE MICROEMULSION GEL[16-17]

Spreadability: Spreadability was performed by using two glass slides of length 7.5 cm. 350 mg of Microemulgel was weighed accurately and it was taken on one glass slide. Another glass slide was placed above it from a height of 5 cm. A weight of 5 gm was kept on the upper slide and after 1 min, diameter of circle that was spread was noted in cm. The observed diameter indicates the type of gel.

Viscosity and Rheological studies: Brookfield digital viscometer (Model LVDV–E, USA) was used for the determination of viscosity and rheological properties of microemulsion based gel using spindle no 6. 10gm of sample was taken into a small sample holder and the viscosity of gel was measured at a temperature of 25 °C.

Determination of pH: The apparent pH of the gel was determined by pH meter in triplicate at 25±1ºC.

Determination of % drug content: For the determination of drug content 1 gm of gel formulation as weighed in 10 ml volumetric flask and dissolved in methanol. It was diluted appropriately and analyzed spectrophotometrically at 272 nm.

***In vitro* release studies:** An *In vitro* drug release study was performed using diffusion cell. Egg membrane was placed between receptor and donor compartments. Microemulsion gel equivalent to 0.2gm was placed in the donor compartment and the receptor compartment was filled with phosphate buffer pH 6.8. The diffusion cells were maintained at 37 ± 0.5℃ with stirring at 100 rpm throughout the experiment. At fixed time interval, 5ml of sample was withdrawn for every 1,2,4,6,8,10 and 12 hrs. and same volume was replaced with receptor fluid solution in order to maintain sink condition. The collected samples were analyzed by UV spectrophotometer at λ max 272nm.

RESULTS AND DISCUSSION

The Miconazole nitrate melting point was found to be 178℃ by Theil's method and 180.27℃ by DSC method which complied with standard monographs, thus indicating the purity of the drug. FTIR analysis confirmed that there was no chemical interaction between the drug and excipients such as Carica papaya seed oil and Cinnamon oil. For formulation development, a pseudoternary phase diagram was constructed using Tween 80 and propylene glycol at Smix ratios (1:1, 2:1, and 3:1) to identify the microemulsion region. Increasing the surfactant ratio expanded the microemulsion zone. Based on this, suitable proportions of oil, Smix, and water were selected for formulation. The prepared microemulsions were clear, transparent, and stable, with % transmittance above 90%, confirming nanometric droplet size. The viscosity ranged from 13–15 cps, showing Newtonian flow, while pH values (5.9–6.5) were within the skin-compatible range. The drug content was uniform (93–98%), and zeta potential values indicated stability without aggregation. The globule size (around 70 nm) and SEM images confirmed smooth, spherical droplets. No phase separation was observed after centrifugation, confirming good physical stability. In vitro drug release studies revealed sustained release for 12 hours, with 95.86% release from CPM3 and 93.98% from CCM3. The release followed zero-order kinetics with a non-Fickian mechanism. Carica papaya seed oil-based formulation showed slightly higher release than Cinnamon oil-based formulation. Stability studies indicated no significant changes, confirming formulation stability. Optimized microemulsions (CPM3 and CCM3) were converted into 1% Carbopol 934-based gels (CPM3-G1 and CCM3-G2). These gels showed good spreadability, suitable viscosity, and pH (6.4–6.6) compatible with skin. The drug content was above 93%, and the gels exhibited sustained release over 12 hours, following zero order kinetics. Stability studies showed no major changes during storage.

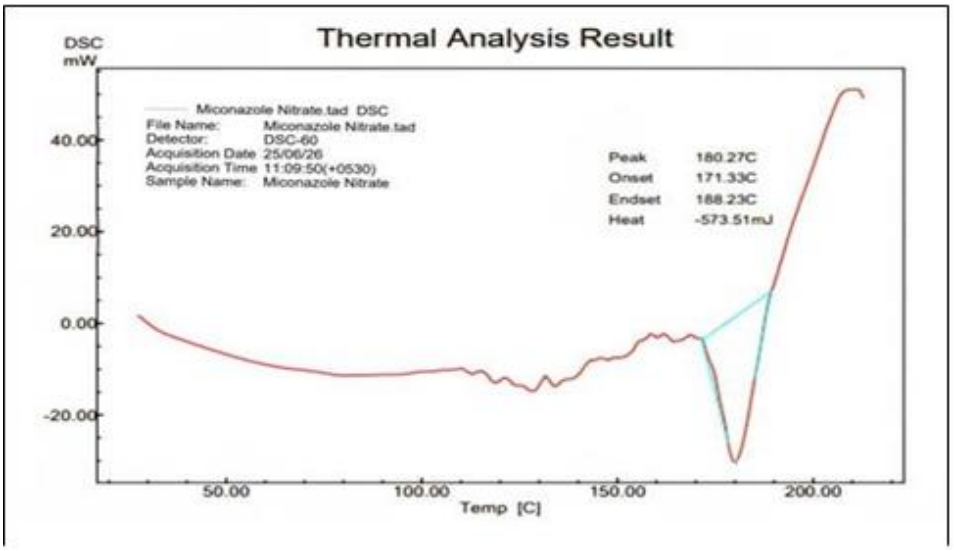

Fig. 1: DSC Thermograph of Miconazole nitrate.

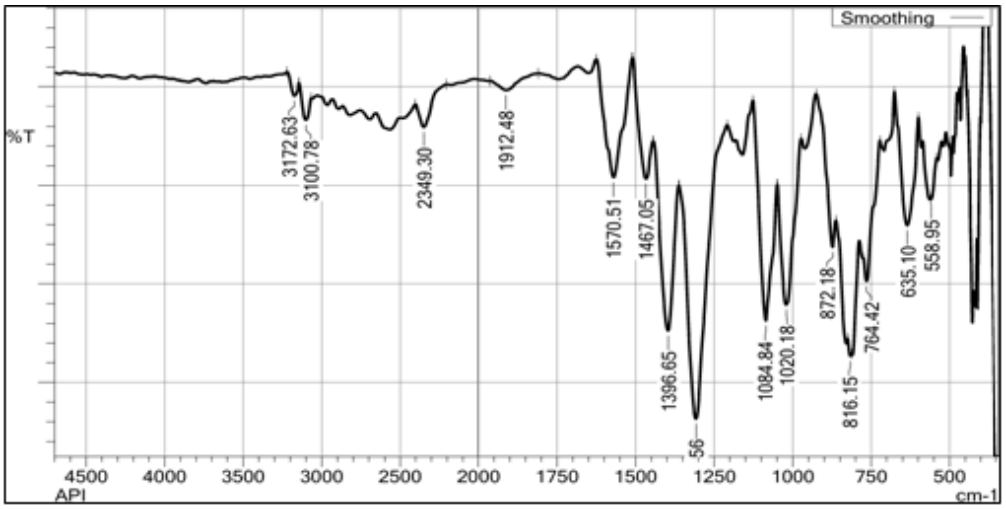

Fig.2: FTIR spectra of Miconazole Nitrate.

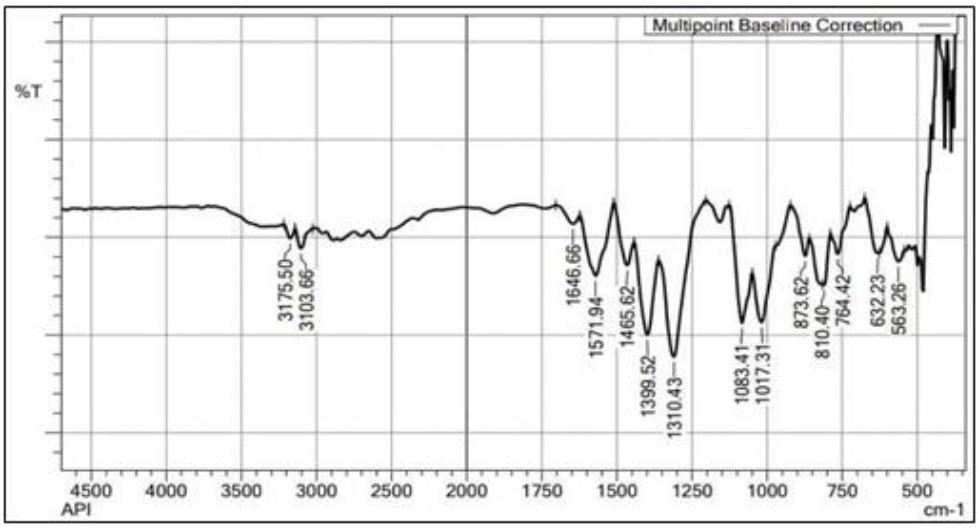

Fig. 3: FTIR spectra of mixture of Miconazole Nitrate and Carica papaya seed oil.

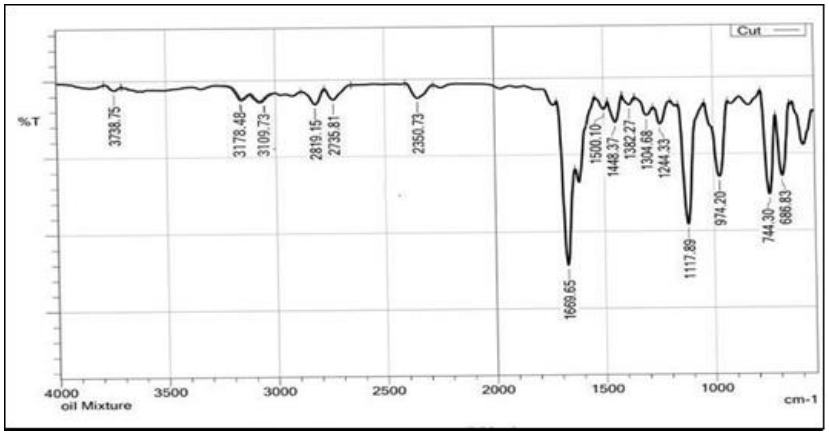

Fig. 4: FTIR spectra of mixture of Miconazole Nitrate and Cinnamon oil.

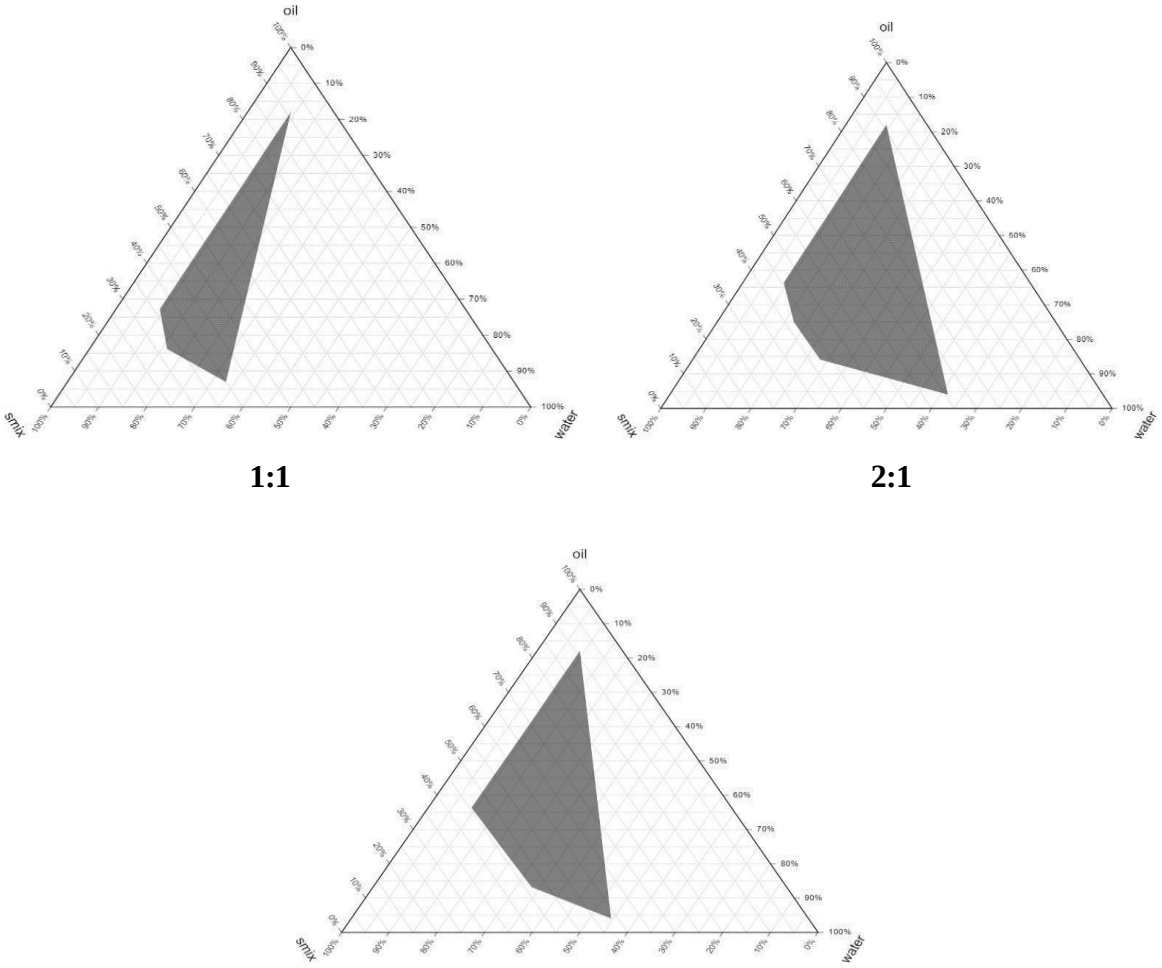

Fig. 5: Pseudoternary phase diagram of Carica papaya seed oil, Tween 80, propylene glycol contains different Smix ratio (1:1, 2:1 and 3:1).

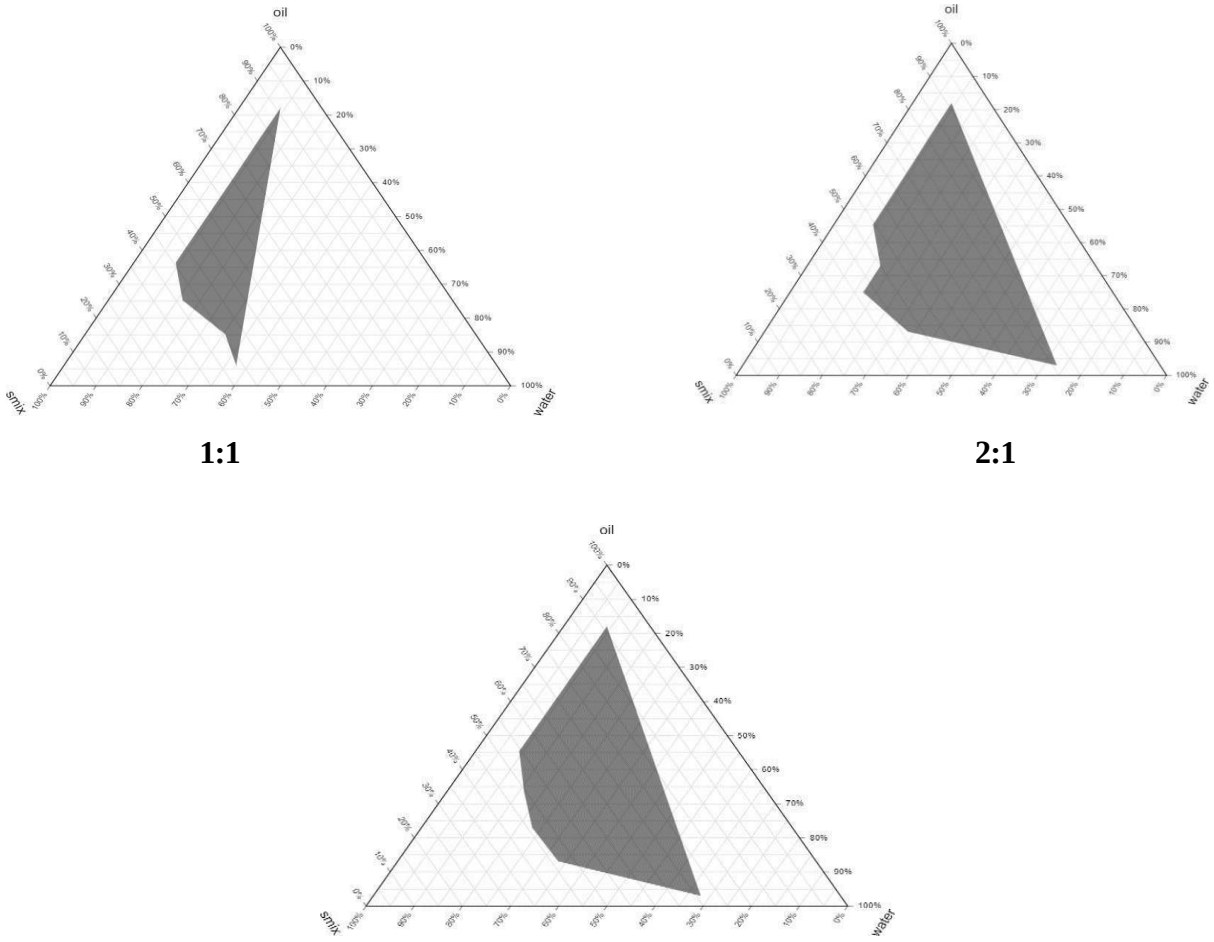

Fig. 6: Pseudoternary phase diagram of Cinnamon oil, Tween 80, propylene glycol contains different Smix ratio (1:1, 2:1 and 3:1).

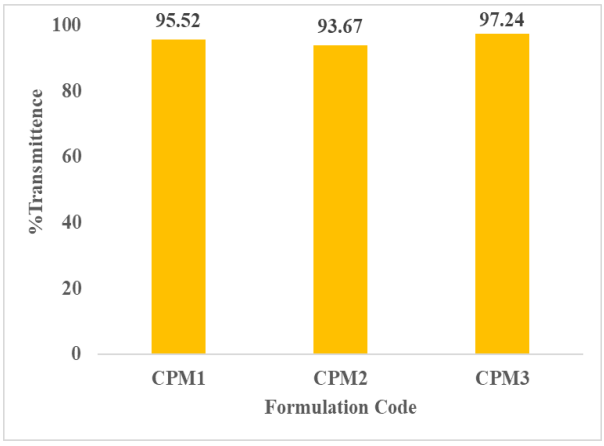

Fig. 7: % Transmittance of CPM1-CPM3.

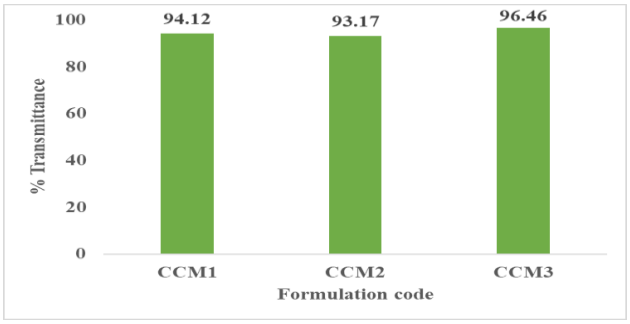

Fig. 8: % Transmittance of CCM1-CCM3.

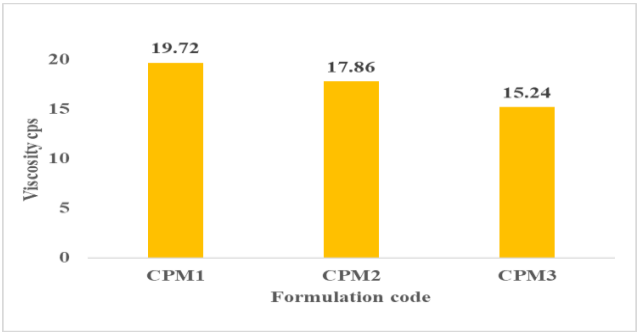

Fig. 9: Viscosity of CPM1-CPM3.

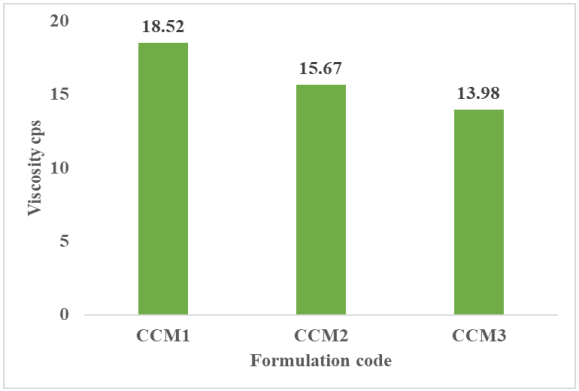

Fig. 10: Viscosity of CCM1-CCM3.

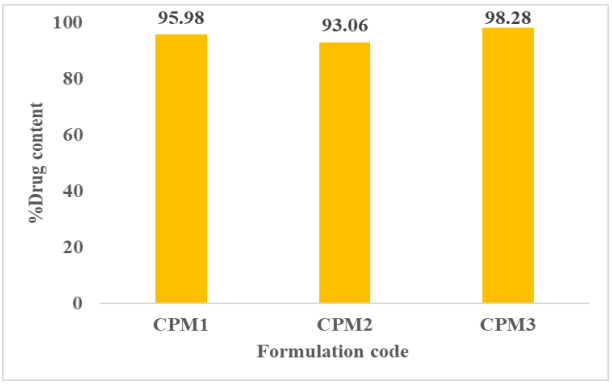

Fig. 11: % Drug content of CPM1-CPM3.

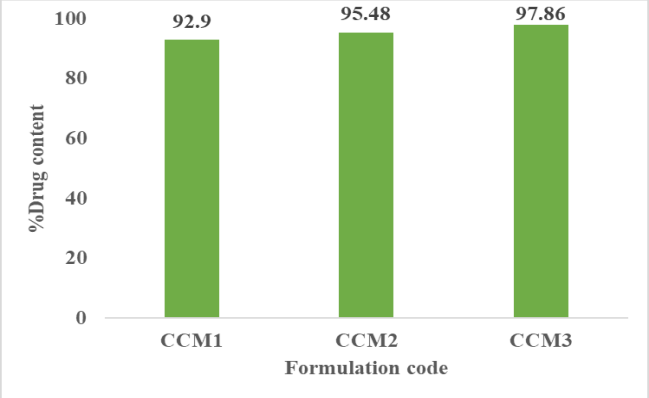

Fig. 12: % Drug content of CCM1-CCM3.

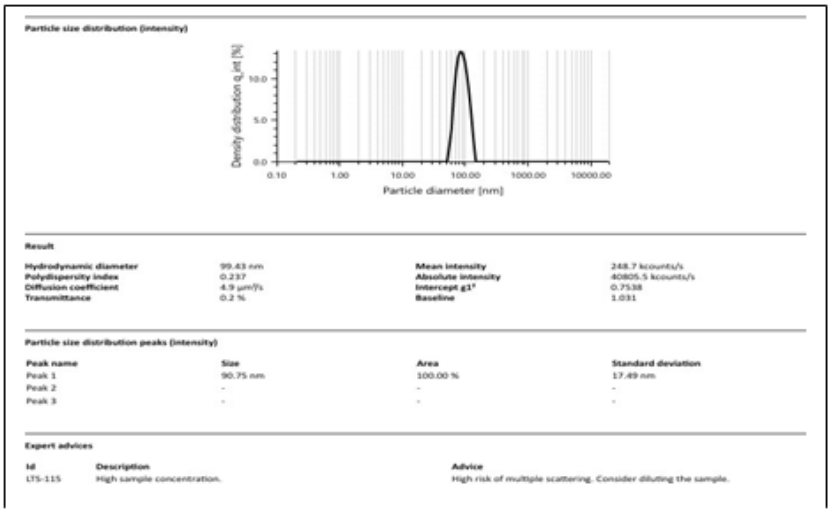

Fig. 13: Globular size of CPM3.

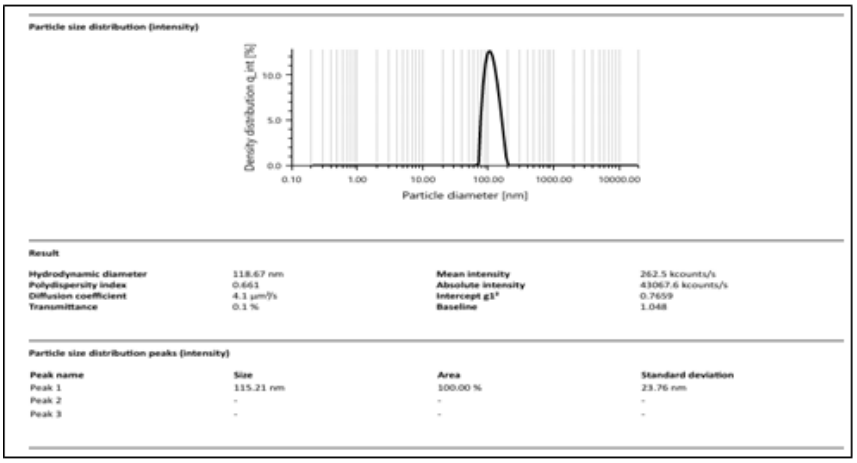

Fig. 14: Globular size of CCM3.

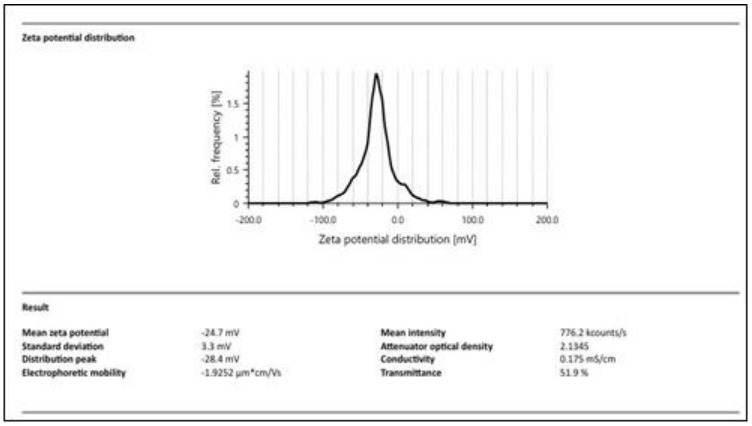

Fig. 15: Zeta potential of CPM3.

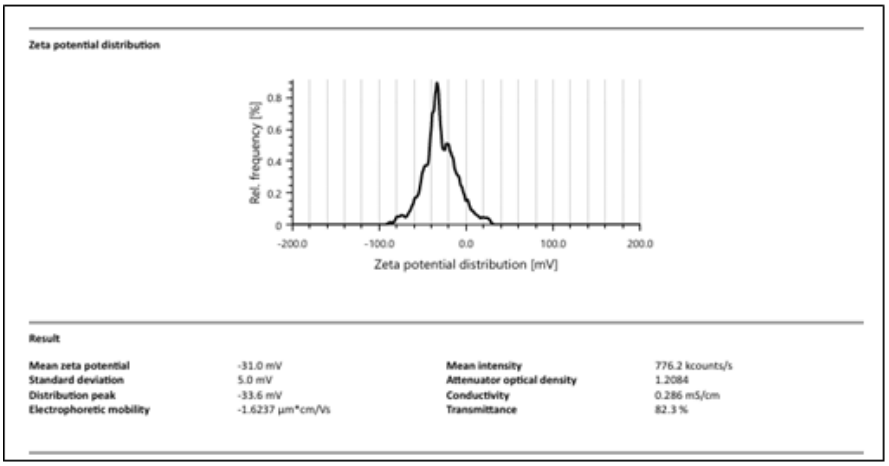

Fig.16: Zeta potential of CCM3.

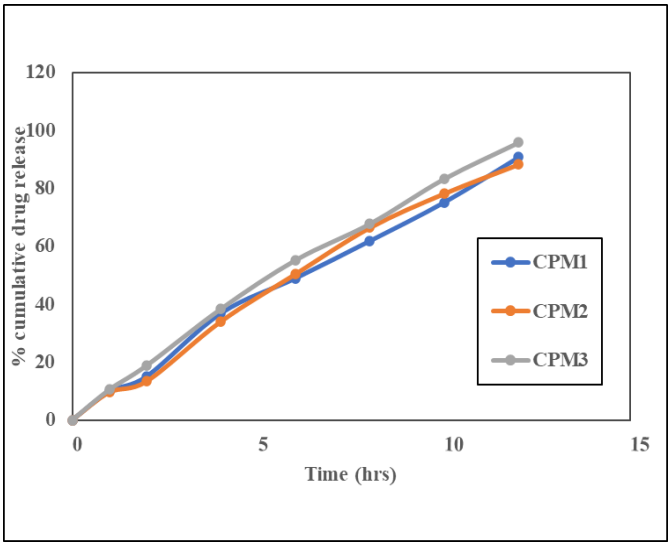

Fig. 17: Comparison of %CDR of CPM1-CPM3.

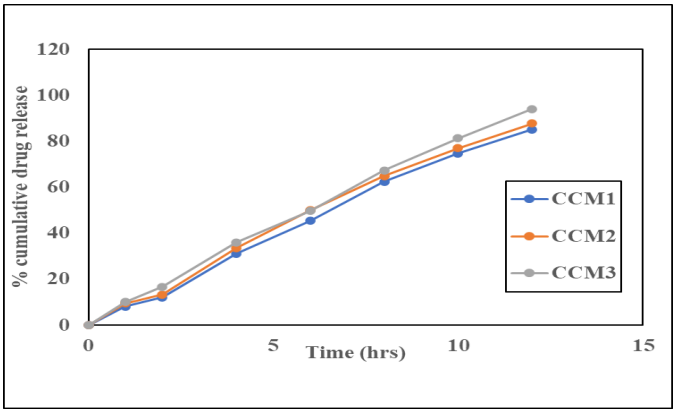

Fig. 18: Comparison of %CDR of CCM1-CCM3.

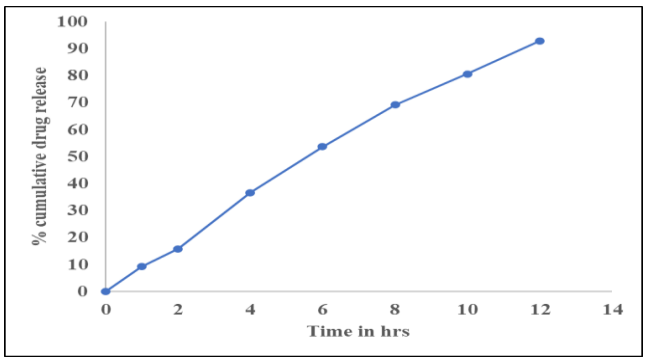

Fig.19: % CDR of CPM3-G1.

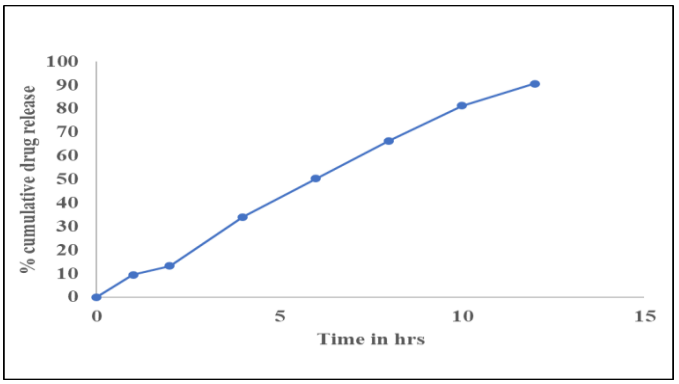

Fig.20: % CDR of CCM3-G2.

CONCLUSION

FTIR analysis confirmed no significant interaction between the drug and excipients. Pseudo-ternary phase diagrams were successfully constructed, and microemulsions were prepared by titrating various oil-to-Smix ratios with water. Among all, formulations CPM3 and CCM3 were optimized due to their high transmittance, suitable viscosity, high drug content, and pH values around 6.4, with better drug release profiles. These were selected for stability testing and gel preparation using 1% w/w Carbopol 934. The resulting gels showed good

spreadability, appropriate pH, high drug content, and acceptable viscosity. In vitro drug release studies indicated that CPM3-G1 and CCM3-G2 provided sustained drug release over an extended period.

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