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Development and Study of Microemulaion Containing Ciproflaxacin with Clove Oil for Antibacterial Activity

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ABSRTACT: The aim of present study is preparation and evaluation of Ciprofloxacin microemulsion along with Clove oil to achieve the synergistic antibacterialactivity. Ciprofloxacin is a broad-spectrum antibiotic with activity against many pathogenic Gram-negative and Gram-positive bacteria, essential oil is used in the formulation to reduce the concentration of drug and achieve the better therapeutic effect. Developed a Pseudoternary phase diagram to find out the microemulsion existence regions by using Clove oil (oil), tween 20 (surfactant), propylene glycol (co-surfactant) by water titration method (ternaryplot.com software). Prepared 3 formulations (CCM1-CCM3) by changing the oil and Smix ratios. Developed microemulsions was characterized for various parameters like %transmittance, viscosity, pH, drug content, surface morphology, zeta potential, in vitro drug release study, release kinetics study. The optimum formulation CCM3 showed higher %transmittance 99.16±0.14, lesser viscosity 12.24±0.24cps, comfortable pH 6.57±0.033, and high % drug content 98.98±0.56. 289.6nm of globule size, zeta potential found to be -3.83mV, and high in vitro drug release 93.01% after 6 hrs. and fallows the zero-order kinetics. The optimized formulation further converted into Microemulgel by dispersing the microemulsion to 1% Carbopol gel base and evaluated for various parameters. The antibacterial efficacy was carried out for optimized microemulsion and it's Microemulgel by agar well diffusion method against Streptococcus aureus and compared with standard drug, CCM3 and CCM3-G showed a better antibacterialactivity than standard drug, it proved that the synergistic activity could be achieved bybothCiprofloxacin with Clove oil microemulsion and microemulgel.

KEY WORDS: Microemulsions, Pseudoternary phase, Ciprofloxacin hydrochloride, Topical drug delivery,Clove oil.

I. INTRODUCTION:

Microemulsion has many advantages compared to emulsions, among others, have stability in the long term by thermodynamics, clear and transparent, can be sterilized by filtration, the manufacturing cost is cheap, has high solubility and has good penetrating capability. One of the most important components of a microemulsion forming was surfactants. The combined use of surfactant and co-surfactant can improve the dispersion of oil in water. [1]The skin provides a remarkably good barrier against bacterial infections. Although many bacteria come in contact with or reside on the skin, they are normally unable to establish an infection. When bacterial skin infections do occur, they can range in size from a tiny spot to the entire body surface. They can range in seriousness as well, from harmless to life threatening.Bacterial skin infections develop when bacteria enter through hair follicles or through small breaks in the skin that result from scrapes, punctures, surgery, burns, sunburn, animal or insect bites, wounds, andpre-existing skin disorders. People can develop bacterial skin infections after participating in a variety of activities, for example, gardening in contaminated soil or swimming in a contaminated pond, lake, orocean. [2] Topical antibiotics are medicines applied to the skin to kill bacteria. The skin is readily accessible and topical agents can be applied at high concentration, achieving effective levels locally with little systemic toxicity. The high local levels of antibiotic that can be achieved with topical formulations can help kill bacteria in bacterial biofilms.[3]The colloidal-based drug delivery systems include nanoparticles, microemulsions, nanoemulsions, nanocapsules, nanovesicles, transferosomes, liposomes, and hydrogel systems. Among all these drug delivery systems, the microemulsions based drug delivery has proven to be a thermodynamically stable and clinically beneficial system because of its versatileness, biocompatibility, and ability to penetrate a drug

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molecule to deep layers of skin due to unique hydration properties of microemulsion ingredients as well as the longer shelf life of formulation. [4]

One of the most used antibiotics against Staphylococcus aureus is Ciprofloxacin [1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperaziny-1-yl) quinolone3-carboxylic acid], a broad-spectrum antibiotic with activity against many pathogenic Gram-negative and Gram-positive bacteria, including Staphylococcus aureus, via DNA gyrase inhibition. Ciprofloxacin (CIP) was suggested for the topical treatment of acute otitis media, acute conjunctivitis and keratitis. Due to the fact that the skin presents limitations such as poor retention and low permeability of the stratum corneum layer, the development of dermal formulations containing CIP has been attempted and proved successful as adjuvant treatment of skin infections**.** [5]

Essential oils are illustrious antibacterial, antifungal, antioxidant, antigiardial and antidiabetic agents. Different essential oils and oil-based formulations are reported to be efficient antimicrobial agents that can be used to prevent food spoilage. The antibacterial activity may be due to the ability of oil components to damage the bacterial membranes and hence resulting in lysis of the cell[6]

Essential oils are prescribed for a variety of health issues by traditional systems of medicine, all over the world. Various pharmaceutical and biological activities like, antibacterial, antibacterial, anticancer, antimutagenic, antidiabetic, antiviral, anti-inflammatory etc., Because of the Antibacterial properties showed by essential oils, the aromatherapy has been used for treatment of serious skin diseases.[7] Hence, in the present work an attempt to study the Antibacterial effect of Ciprofloxacin hydrochloride along with (essential oil) Clove oil to be formulated as microemulsion and explore the synergetic Antibacterial effect.

II. MATERIALS AND METHODS:

Materials: Ciprofloxacin hydrochloride was gifted by (yarrow chem products, Mumbai India). Tween20, Tween80(Thomas baker PVT LTD, Mumbai),propylene glycoland methanol (S D Fine chemicals Mumbai), Carbopol 934(Central drug house, New Delhi), Clove oil purchased from (Swastik oil. Co., Ooty), Clove oil purchased from (Heilen bio pharm, Gujarat).

Methods:

Solubility studies of Ciprofloxacin hydrochloride:

Solubility determination in the different oils, surfactants and co-surfactants for formulating micro emulsion drug delivery system. The solubility of the drug in various oils is an essential step for the microemulsion formulation. So before starting the phase diagram one must have to choose the oil, surfactant and co-surfactant in which the drug shows maximum solubility, to be in the desired solubility range, which is required for the formulation of micro emulsion drug delivery system. Drug powder of Ciprofloxacin hydrochloride was added in excess to each of the oils, surfactants (S), co-surfactants (CoS) and then vertexed for mixing. After vertexing the samples were kept for 72 hours at ambient temperature for attaining equilibrium. The equilibrated samples were then centrifuged at 5000 rpm for 30 minutes to separate the undissolved drug. The supernatant was taken and diluted with Water and observed by UV spectrophotometric method at 270nm. [8].

Construction of Pseudoternary phase diagram:

To find out the existence range of microemulsions, pseudo ternary phase diagrams were constructed by utilizing water titration method at ambient temperature (25 ºC). Based upon on the available solubility profile of the drug, Clove oil was selected as an oil phase, Tween20 and propylene glycol were used as surfactant and co-surfactant respectively. The Smix (surfactant+Co-surfactant) ratios were selected to be 1:1, 2:1 and 3:1 w/w and used. For each phase diagram at specific Smix concentration the Clove oil was added from the range of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1(%w/w) and the mixture were diluted with distilled water by sequential addition of 0.1ml of water using a micropipette. Water was added drop by drop while blending on a magnetic stirrer at room temperature, and the samples were marked as being visually clear or turbid. The microemulsion regions were recognized as transparent and isotropic mixtures. The percentage of three different phases, that is oil, water, and the mixture of surfactant and co-surfactant were calculated (Table 2). From the endpoint compositions of titrated samples, the mass percent composition of the components like oil, Smix and water was calculated and then plotted on ternaryplot.com to construct the pseudo ternary phase diagram. [9].

Preparation of Ciprofloxacin hydrochloride loaded microemulsion: Dissolve the drug infixed

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ratios of Smix and then add oil, vertex the mixture for 15minutes continuously. Then add require quantity of water drop wise drop with stirring and allow to forming a clear transparent liquid, it shows formation of a microemulsion. Finally, the prepared microemulsions formulation incorporated to 1%w/w Carbopol 934 gel base. [10]

Evaluation of Ciprofloxacin hydrochloride microemulsion.[11-16]

1. Percenttransmittance:

The transparency of the microemulsion was determined by measuring the percentage transmittance at 650nm against distilled water as blank by using UV spectrophotometer (UV 1800, Shimadzu, Japan).

%T= Antilog (2-Absorbance)

2. pH and Viscositymeasurements:

The Rheological behaviour of the microemulsion formulation was evaluated using an Ostwald viscometer at a room temperature. The pH of Ciprofloxacin hydrochloride microemulsion formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicate and standard values were calculated.

3. %Drugcontent:

For the determination of drug content about one ml of each microemulsion formulationwas transfer to a 10 ml volumetric flask and dissolved in Water. It was diluted appropriately and analyzed spectrophotometrically at 270 nm.

4. Measurementofglobule sizeand zetapotential:

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

5. Surfacemorphology:

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

6. Centrifugation test:

The optimized microemulsion formulation CCM3 was centrifuged at 3500 rpm for 30 min to ensure physical stability.

7. Invitrodiffusionstudy:

In invitro diffusion study, the diffusion medium used was phosphate buffer pH 7.4. Assembly of diffusion cell for invitro diffusion studies the diffusion cell was planned as per the dimension given. Diffusion cell with an effective diffusion area of 3.14 cm2 was used for invitro permeation studies. The diffusion cells were deposited on the magnetic stirrers. The donor compartment consisting of 1 gm. of microemulsion containing Ciprofloxacin hydrochloride. The receptor compartment was filled with fluid. Then 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 speed of the stirring was kept constant all over the experiment. With the help of 1ml pipette 1 ml of sample was withdrawn at a time interval of 60 min from sampling port of receptor compartment and same volume was the replaced with receptor fluid solution in order to continue sink condition. The samples were appropriately diluted and the absorbance was measured at 270 nm using UV spectrophotometer.

Evaluation of prepared microemulsion gel[17-19]

1. Spreadability:

Spreadability was performed by using two glass slides of length 7.5 cm. 350 mg of Microemulgel was weighed exactly and it was taken on one glass slide. One more 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 detected diameter indicates the type of gel.

2. Viscosity and rheological studies:

Brookfield digital viscometer was used for the determination of viscosity and rheological properties of microemulsion based gel. The viscosity of gel was measured at discrete angular velocities at a temperature of 25 °C.

3. Determination of pH:

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

4. 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

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spectrophotometrically at 270 nm.

5. Invitrodrug release studies:

An invitro drug release study was performed using diffusion cell. Egg membrane was laydown 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 7.4. 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 1,2,3,4,5 and 6 hrs. and same volume was replaced with receptor fluid solution in order to continue sink condition. The collected samples were analyzed by UV spectrophotometer at λ max 270nm.

6. Stability studies:

The prepared gel (CCM3) was subjected to stability study for a period ofthree months at room temperature.

7. In vitroAntibacterial activity studies:

Antimicrobial activity of given samples was investigated using well diffusion method. Test plates (diameter 10 cm) were prepared with 20 mL of respective Nutrient media. After media get solidified, 100 µL of 24 h culture (1.5×10^8 CFU/mL) was added and uniformly spread over plates using L shaped rod. Well (about 6mm diameter) were made and the given 8 samples were added in given concentrations in respective wells. And also, the wells 30µg/40µL Streptomycin (for bacteria) was used as a commercial standard. Plates were incubated at respective were measured and recorded after the incubation time. The inhibitory zone was considered the shortest distance (cm) from the outside margin of the samples to the initial point of the microbial growth. Growth conditions for 24 h. Zones of inhibition of microbial growth around the well.

III. RESULTS AND DISCUSSIONS

Solubility study of Ciprofloxacin hydrochloride

Based on the Ciprofloxacin hydrochloride solubility study data, the oil, surfactant, and co-surfactant components were selected in the present research work. Ciprofloxacin hydrochloride has shown the highest solubility in water (46.11±0.19) propylene glycol (15.92±0.68)tween 20 (8.97±0.078) Clove oil(7.59±0.16 mg/mL), methanol (0.083±0.003 mg/mL) and clove oil (8.51±0.15mg/mL) components among the various oils, surfactants and co-surfactants. Table 1 summarizes the solubility data for Ciprofloxacin hydrochloride by UV method.

Construction of Pseudoternary phase diagrams

The pseudo ternary stage charts of different proportions of surfactants (Tween 20) Co-surfactant (Propylene glycol) were utilized to develop. The Smix weight proportions [1:1, 2:1, 3:1] are addressed in Fig.1 and Table 2, in pseudo-ternary stage graph where microemulsion regions are noticed by using Ternary plot.com software.

Table 1. Solubility profile of Ciprofloxacin hydrochloride

Phasetype	Excipient	Solubilitymg/ml
Aqueous	Water	46.11 ±0.19
Organicsolvent	Methanol	0.083±0.003
Oils	Clove oil	7.59 ± 0.16
	Clove oil	8.51 ± 0.15
	Thyme oil	3.73±0.12
Surfactants	Tween20	8.97±0.078

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	Tween80	2.90±0.72
Co-Surfactants	Propylene glycol	15.92±0.68
	Poly ethylene glycol 400	1.78±0.012
Phosphatebuffers	pH 6.8	0.12±0.002
	pH 7.4	0.10±0.001

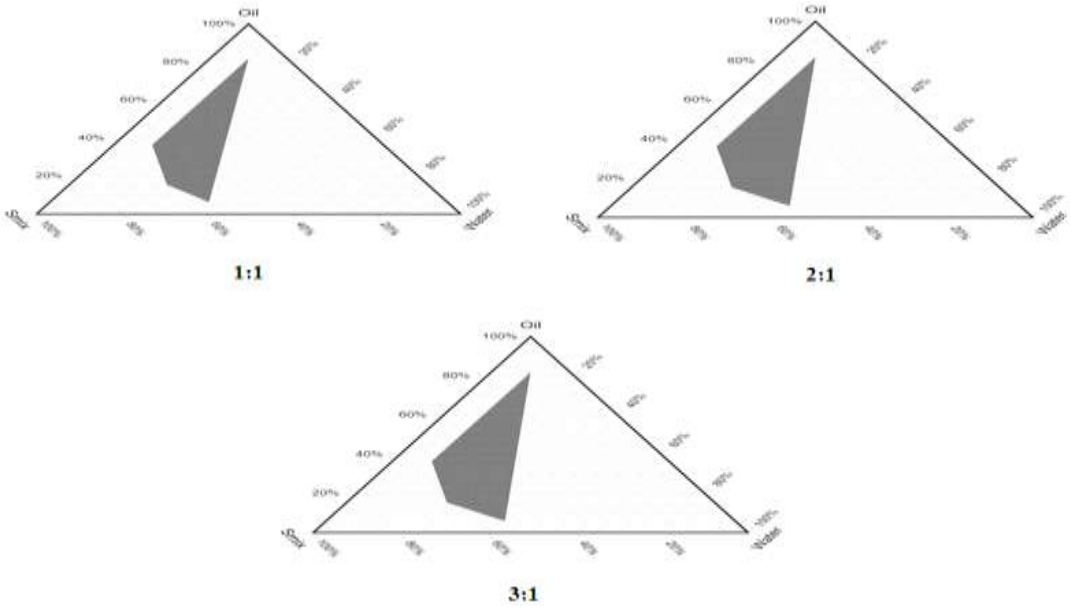

Fig 01: Pseudoternary phase diagram of Clove oil, Tween 20, propylene glycol contains different Smix ratio (1:1, 2:1 and 3:1).

Table 2: Formulation development of Ciprofloxacin hydrochloride microemulsion with selected oil, Smix, water from the Pseudoternary phase

Formulation code	**Smix ratio**	**Surfactant**	**Oils**	**Percent w/w component in formulation**			
				Oil %	**Smix %**	**Water%**	**Drug %**
CCM1	1:1	**Tween 20**	**Clove oil**	15	55	30	1
CCM2	2:1			20	50	30	1
CCM3	3:1			35	50	15	1

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Evaluation of microemulsion

- **% Transmittance:**Clarity of microemulsion was checked by % transmittance. The transmittance values of all formulations are above 90% as shown in Table 3. The CCM3 formulation showed 99.16±0.14 compare to other formulations.Which indicates that the microemulsions were clear and transparent in nature also indicates the globules in the formulation is in the nanometer range.
- **pH and viscosity measurements:**The pH of all the formulations is found in the range of 5.95 to 6.57 as shown in Table 3. This is well between the ranges for topical administered formulation. Formulation of CCM3 has shown pH 6.57±0.033. Therefore, there is no need for adjusting the pH of the formulation. The viscosity of microemulsion formulation was determined as shown in Table 3, all samples exhibited Newtonian flow behaviour and formulation CCM3 showed12.24±0.245cps shows less viscous compared to other microemulsion formulations.
- **Drug content:** The drug content of all the formulations of Ciprofloxacin hydrochloride microemulsion is shown in Table 3. CCM3 was exhibited 98.98±0.56% higher drug content than other formulations. The microemulsion drug content of all formulations was found to be within the range of 92-98% which was within the limits of USP specifications. it indicates uniformity in drug content without any degradation.

Table 3: Evaluation of Ciprofloxacin hydrochloride microemulsion CCM1-CCM3

Formulation code	%Transmittance	Viscosity	pH	%Drug content
CCM1	92.29±0.14	13.54±0.685	5.95±0.053	92.42±1.74
CCM2	96.93±0.10	16.44±0.519	6.23±0.079	96.03±0.56
CCM3	99.16±0.14	12.24±0.245	6.57±0.033	98.98±0.56

Measurementofglobule sizeand zetapotential: Theglobule size and zeta potential were measured by a Malvern zeta analyzer and it was Found that 289.6nm for CCM3 (Fig 2). Confirmed that ME are within the required size ranges. The Zeta potential of microemulsion CCM3 was found to be -3.83 Mv (Fig 3) which indicates that the globules aggregation is not expected to take place so, they are sufficient to be stable.

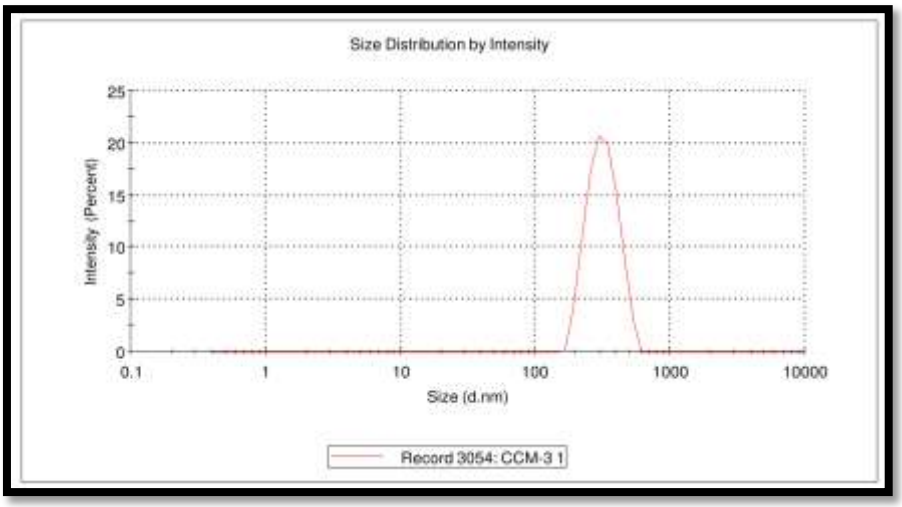

Fig 02: Globule size of CCM-3

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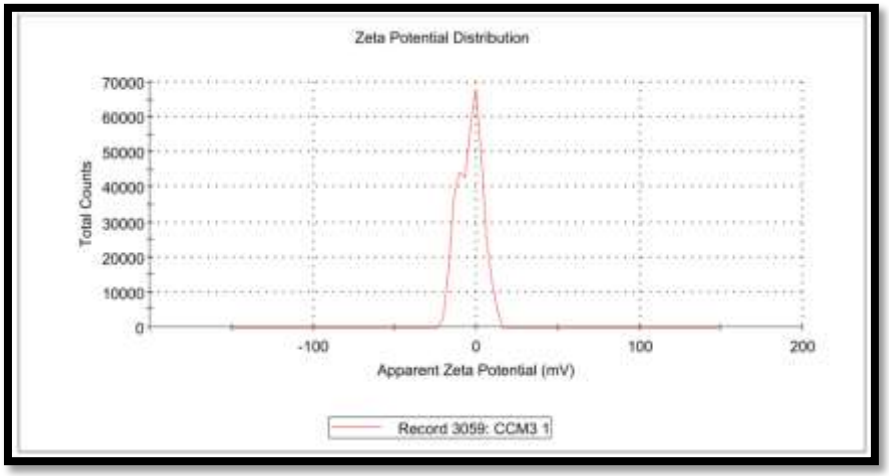

Fig 03: Zeta potential of CCM-3

- **Surfacemorphology:** The surface morphology was studied by SEM for the optimized formulations which were confirmed that the drug is completely dissolved. This can have the ability to form a microemulsion. And the particles are globular with globule size in the nanometre scale with a smooth surface as shown in Figure 4, for CCM3.

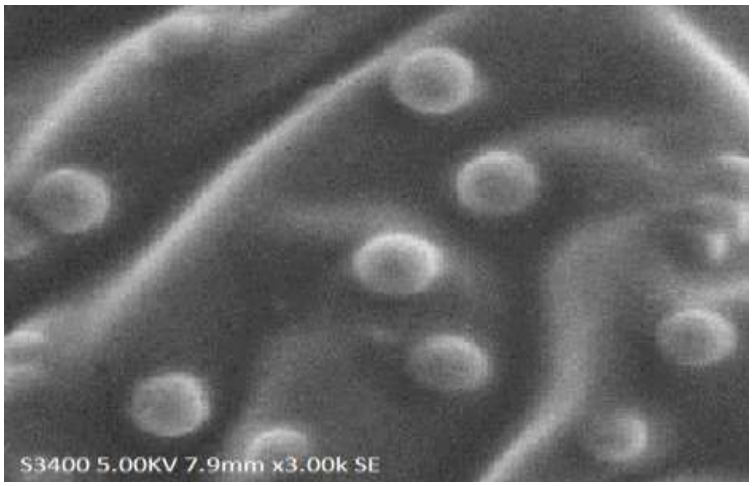

Fig 04: SEM image of CCM3

- **Centrifugation test:** There is no phase separation of optimized microemulsion formulation. Consequently,CCM3formulation will be monophasic in nature.
- **Invitrodiffusionstudy:** From the in vitro release studies, we observed that 0 - 20% of the drug was delivered in 1hrs and over half drug released in 3 hrs. and more than 80% of the drug released in 6 hrs. The formulation ofCCM3 showed 93.01% (Figure 5). And it has shown a higher % of drug release when compared with other formulation. (Table 4).

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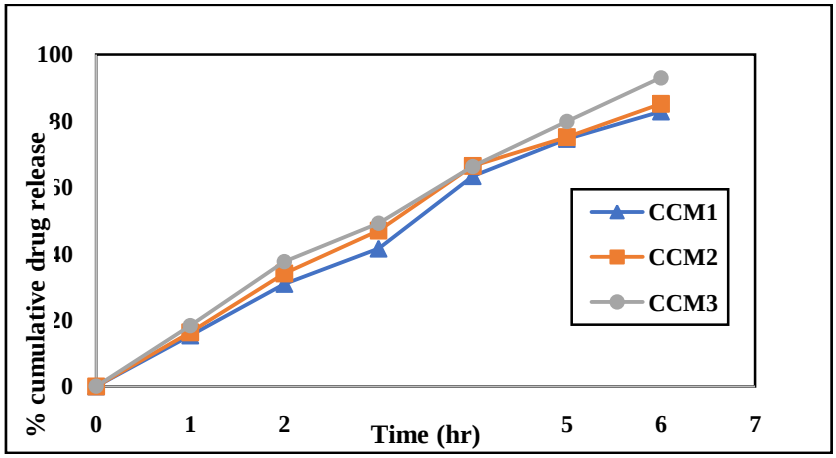

Fig 05: Comparison of % cumulative drug release of CCM1-CCM3

Table 4. Invitro diffusion study of Clove oil microemulsion

Time in hrs	%CDR		
	CCM1	CCM2	CCM3
0	0	0	0
1	15.33	16.0	18.28
2	30.87	34.02	37.56
3	41.49	47.00	49.16
4	63.32	66.47	66.27
5	74.53	75.12	79.84
6	82.79	85.15	93.01

Evaluation of microemulsion based gel

- **Spreadability:** The spreadability is an important property of topical formulation from a patient compliance point of view. The increase in the diameter due to spreading of the formulation gel CCM3-G1 was found to be 2.63± 0.094cm.
- **Viscosity determination:** The microemulsion gelformulation CCM3-G1 showed 10150 ± 40.82cps. This value indicatesprobable retention of drug formulation on topical surface area without any drainage.
- **pH measurement:** The pH of microemulsion gel CCM3-G1 was found to be 6.74 ±0.04(Table 5) and is suitable for topical application with minimum discomfort**.**
- **% Drug content:** The prepared Ciprofloxacin hydrochloride microemulsion gel CCM3-G1 subjected to drug content uniformity. The microemulsion gel was in the permissible range from 97.60% respectively which indicated the drug uniformly dispersed throughout the formulation.

Table 5: Evaluation of microemulsion gel-based gel

Formulation code	Spreadability	Viscosity cps	pH	% Drug content
CCM3-G1	2.63±0.094	10150 ± 40.82	6.74 ± 0.04	97.60± 0.16

- **Invitro Drug release:** The result of the In vitrorelease of Ciprofloxacin hydrochloride from the gel formulation. However, the results clearly show that the gels can retain the drug for prolonged periods. The % CDR of microemulsion gel formulation CCM3-G1 was found to be 90.26% as shown in Figures 6.

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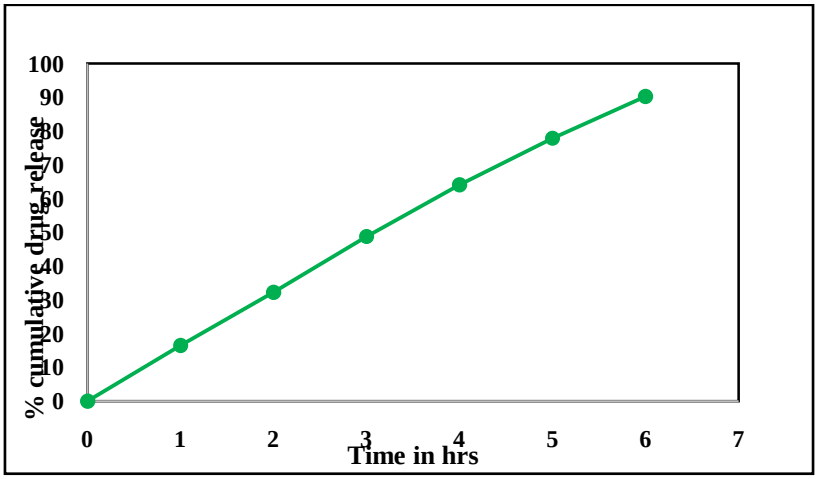

Fig 06: Invitro drug release profile of CCM3-gel

- **Release kinetics studies**: The cumulative amount of drug released from all Ciprofloxacin hydrochloride microemulsion and microemulsion based gel formulations at different time interval was fitted to discrete models to find out the mechanism of drug release. The correlation coefficients table 6 showed that the kinetic of drug release from microemulsion (CCM1-CCM3) (fig: 7- fig11) and(CCM3-G) microemulsion based gel fallowed zero order model of kinetics(fig:8). 'n' values were found to be more than 0.5 this shows that the release approximates non-Fickian diffusion mechanism.

Table 06: Release kinetics of optimized microemulsion and microemulsion based gel

Formulation code	Zero order	First order	Higuchi model	Peppas model	'n'values
	R^2	R^2	R^2	R^2	
CCM1	0.9905	0.9652	0.9216	0.6951	1.7615
CCM2	0.9886	0.9716	0.9399	0.6795	1.7579
CCM3	0.9953	0.9032	0.9403	0.6632	1.7549
CCM3-G	0.9978	0.9983	0.9295	0.688	1.7782

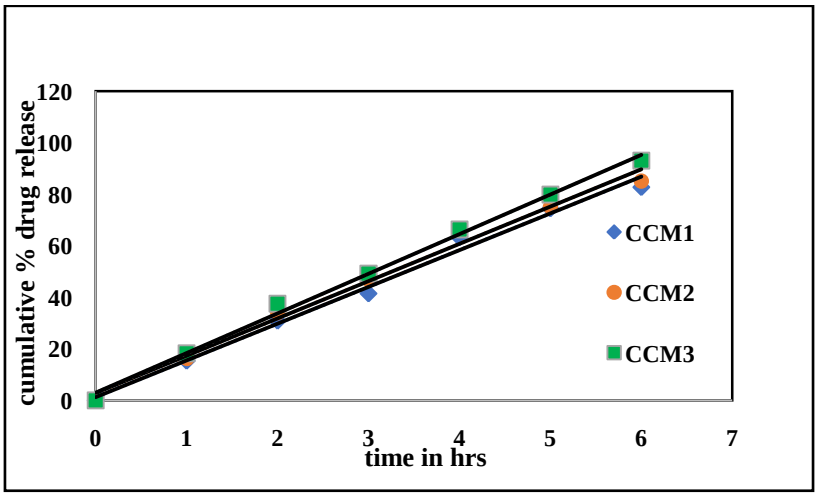

Figure 07: Zero order release kinetic profile of CCM1-CCM3

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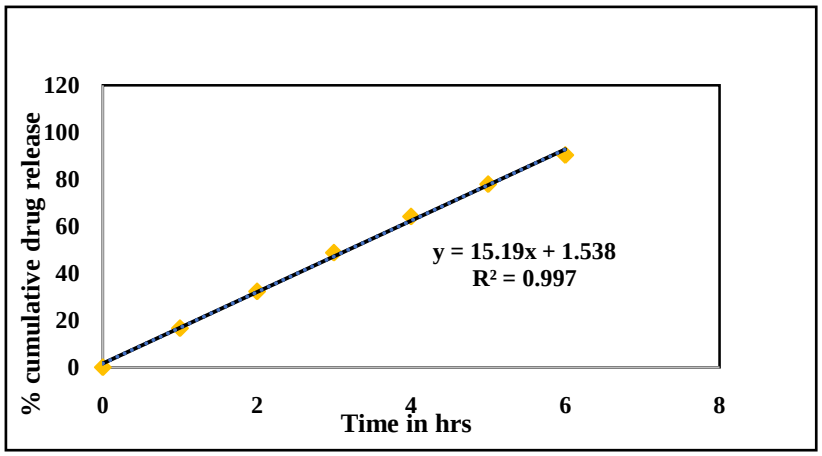

Figure 08: Zero order release kinetic profile of CCM3-G

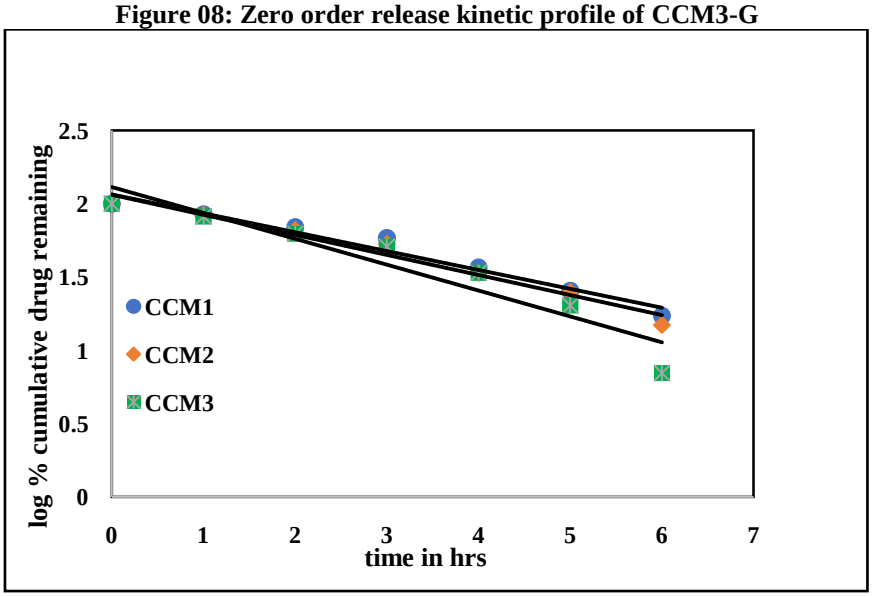

Fig-09: First order release kinetic profile of CCM1-CCM3

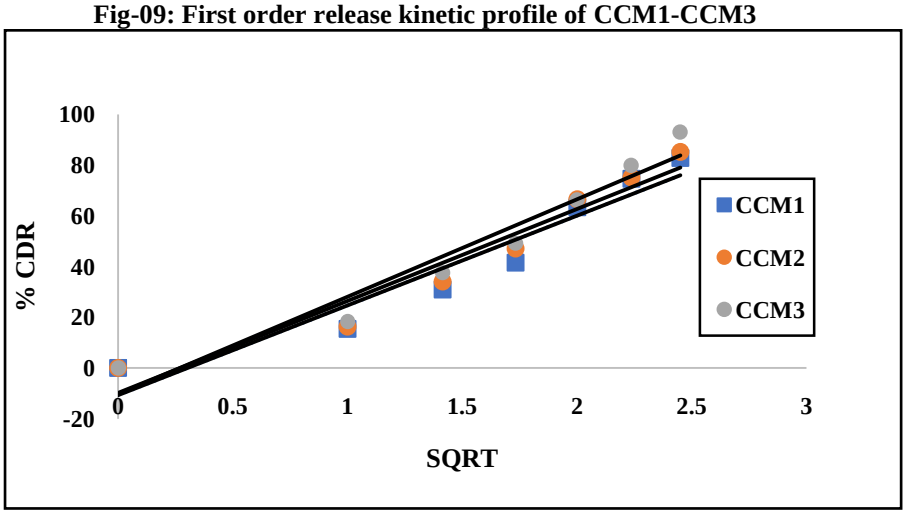

Fig-10: Higuchi release kinetic profile of CCM1-CCM3

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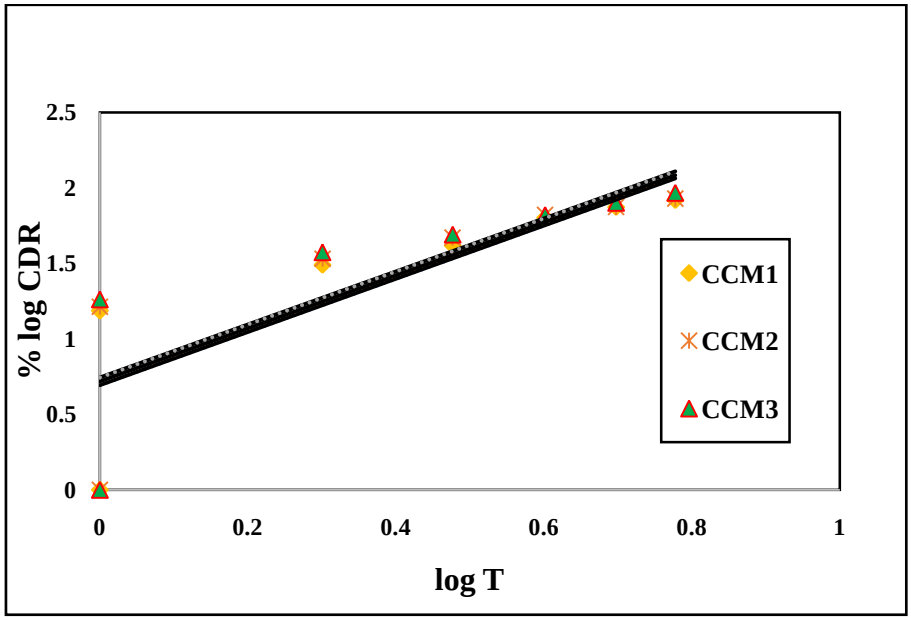

Figure11: Peppas release kinetic profile of CCM1-CCM3

Invitro Antibacterial activity studies: In vitro anti-bacterial effect of optimized formulations, oils and drug was determined by using agar well diffusion method and fungal strain Streptococcus aureus. at concentrations of drug 300µg/ml,50µl of oils, 30µl of microemulsions and 60mg of gels and the results are shown in Table 7 and Figure 12.

Table 7: Report of Antibacterial activity against S. aureus

Sl no	Samples	Quantity Used	Zone of inhibition in mm	Sensitivity
1	Ciprofloxacin	300µg/ml	32	sensitive
2.	CCM-3	30µl	39	sensitive
3.	CCM-3GEL	60mg	36	sensitive
4.	Clove oil	50µl	20	sensitive

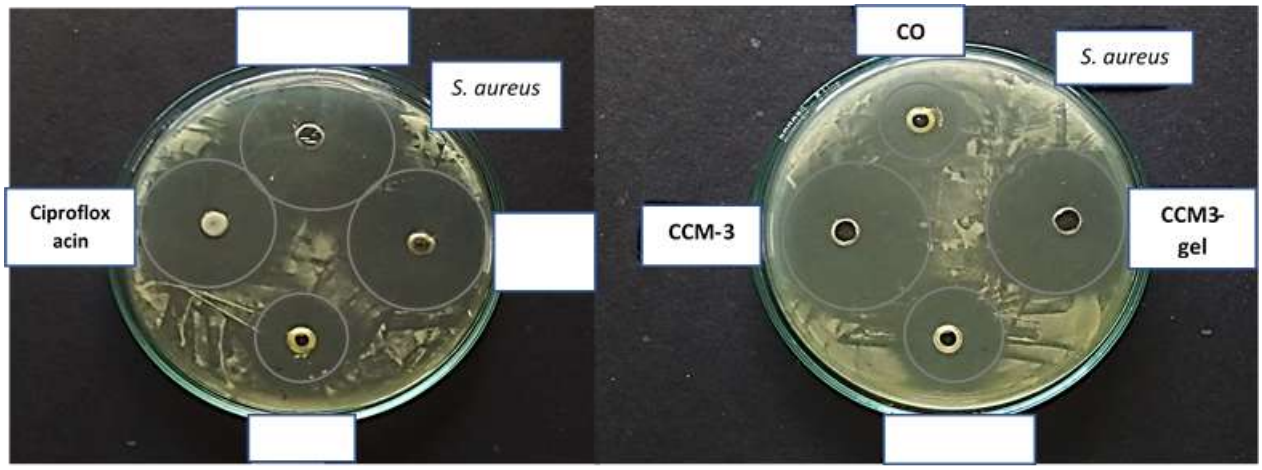

Figure 12: The Antibacterial activity against S. aureus using agar well diffusion method.

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A- Ciprofloxacin, TCM-3, TCM3-G, Tea tree oil.
B-CCM-3, CCM3-G, Clove oil, Tea tree oil + Clove oil

- **Stability studies:** Stability studies of microemulsion gel formulation CCM3-G1 Shows that

Negligible change in drug content and % CDR revealed that the formulations are stable on storage.

IV. CONCLUSION:

Ciprofloxacin hydrochloride microemulsionswith clove oil were prepared and evaluated successfully. The optimized formulation (CCM) showed %transmittance (99.16±0.14), pH (6.57±0.033), drug content (98.98±0.56),viscosity (12.24±0.24cps), invitro release (93.01%).and 289.6nm globule size and -3.83mV zeta potential obtained it indicates formulations are stable. the optimized formulation converted into gel and it shows good spreadability (2.63±0.094), pH (6.74±0.04), drug content (97.60± 0.16), invitro release (90.26) and high viscosity (10150 ± 40.82 it indicates that drug retain for a prolong period of time on surface of skin. The antibacterial activity of optimized microemulsion and its gel shows more antibacterial activity compare to drug and clove oil individually. So, successfully we achieved the synergistic effect of drug and clove oil in the form microemulsions.

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