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Research Article

Formulation and Evaluation of Micro Emulsion for the Treatment of Bacterial Meningitis

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A B S T R A C T

The aim of the present study was to prepare antibacterial drug loaded microemulsion. Antibactrial drug loaded Microemulsion were prepared by water titration method. The microemulsions were further characterized for particle size, zeta potential, pH, viscosity, drugcontent, and in vitro drug release behavior. The results revealed that this method is reproducible, more feasible and led to the entrapment of drug with an expected sustained release. The nanoparticle precipitated was with particle size of 176.8 nm, zeta potential of −29 mV, pH is determined in 4.5 to 6.5 and Viscouse in flow. The Drug content was noted was 83.95%. In vitro release was about 32.16% release in 1 h. When the regression coefficient values were compared, it was observed that 'R2 ' values of first order was maximum i.e. 0.9644 hence indicating drug release from formulation was found to follow zero order release kinetics. Antibactrial drug-loaded Microemulsion may be a good choice for the improvement of bioavailability and reduction in toxicity.

Keywords: CNS-targeted microemulsion, Bacterial meningitis, Blood-brain barrierpermeability, Amphiphilic surfactants in CNS therapy, Neurotherapeutics.

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INTRODUCTION

The effective delivery of active pharmaceutical ingredients (APIs) to the brain is essential for the successful treatment of numerous neurological and psychiatric conditions. Traditional drug delivery routes, such as oral or parenteral administration, require the therapeutic agent to traverse several physiological barriers before reaching the cerebral circulation. Among these, the blood–brain barrier (BBB) represents the principal obstacle, serving as a highly selective and protective interface that shields the brain from potentially harmful external agents, including toxins and pathogens.[1] This barrier is composed of specialized endothelial cells, which exhibit structural and functional characteristics distinct from peripheral endothelial cells. A key determinant of the restrictive nature of the BBB is the presence of tight junctions between adjacent cells in the paracellular space. These junctions are formed by specific transmembrane proteins—such as claudins, occludins, and junctional adhesion molecules—that play a critical role in reducing permeability to hydrophilic compounds, including many pharmaceutical agents.[2]In addition to its structural integrity, the BBB is further reinforced by enzymatic degradation systems, minimal pinocytic activity, and multiple active efflux mechanisms. Among the latter, proteins such as P-glycoprotein and other multidrug resistance-associated proteins actively transport foreign substances out of the brain vasculature, limiting their access to the central nervous system (CNS).[3] As Partridge has emphasized, the challenges associated with traversing the BBB are pervasive, to the extent that they should be considered a standard limitation, given that over 98% of small molecule drugs fail to penetrate this barrier. This is even though physicochemical properties such as low molecular weight (typically under 400 Da) and high lipophilicity are generally considered favourable for BBB permeation.[4,5] Furthermore, the BBB poses a particularly formidable challenge to the delivery of macromolecular therapeutics, which are effectively excluded from crossing this barrier under normal physiological conditions.[6] Consequently, the BBB is widely regarded as the most complex and restrictive biological membrane with respect to drug delivery to the CNS. A summary of the

primary factors influencing BBB permeability is presented below.

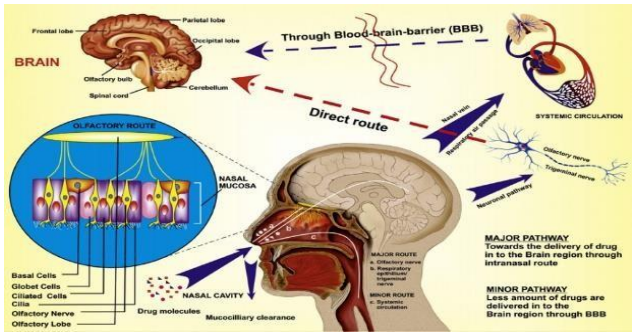


Figure 1: Nasal Drug Delivery

To ensure effective delivery of active pharmaceutical ingredients to the brain, several invasive and semi-invasive techniques have been explored over the years.[7] Invasive strategies include direct intracerebral administration methods.[8] such as bolus injections or continuous infusions into the brain parenchyma.[9] Another approach utilizes intracerebral implants that allow for sustained drug release through biodegradable polymers. An example of such a formulation is Gliadel™ (Eisai Inc.), a polymer wafer containing carmustine, which is implanted into the surgical cavity following the resection of malignant glioma.[10] Alternatively, drugs may be administered directly into the cerebrospinal fluid (CSF) located within the subarachnoid space or the central canal of the spinal cord—an approach known as intranasal drug delivery.[11] Despite their effectiveness, these techniques are inherently invasive and carry a risk of perioperative and postoperative complications, including haemorrhage, catheter misplacement or malfunction, and infections associated with catheter use.[12,13] To circumvent the limitations posed by low permeability of the blood-brain barrier (BBB), less invasive strategies have been developed, such as transient BBB disruption through the administration of hyperosmotic agents [14] or the application of ultrasound.[15] However, in all methods involving temporary BBB disruption, careful consideration must be given to the reversibility and duration of tight junction opening to ensure both therapeutic efficacy and patient safety, particularly with repeated treatments. It is also crucial to recognize that increasing BBB permeability may inadvertently expose the central nervous system to potentially harmful exogenous substances.[16]

INTRODUCTIONOFMICROEMULSION

The micro emulsion concept was introduced as are molecularly Dispersed. Most researchers in the Early as the 1940s by Hoar and Schulman who field agree however that for a micro emulsion to Be Generated a clear single-phase solution by titrating a formed it Is important that the system contains some Milky emulsion with Hexanol.[17] Schulman co workers (1959) subsequently coined the Term microemulsion.[18] and it has since been defined and indeed Redefined on many occasions. For the purposes of this review, However, the microemulsion definition provided by Danielsson and Lindman in 1981 will be used as the point of reference.[19] Microemulsions are thus defined as a system of water, oil and Amphiphile which is a single optically isotropic and Thermodynamically stable liquid solution In practice, the key Difference between emulsions and micro emulsions are that the Former, whilst they may exhibit excellent kinetic stability, are Fundamentally thermodynamically unstable and will eventually Phase separate.[20] Another important difference concerns their Appearance; emulsions are cloudy while micro emulsions are Clear or translucent. In addition, there are distinct differences In Their method of preparation, since emulsions require a large Input of energy while micro emulsions do not. The latter point has Obvious implications when considering the relative cost of Commercial production of the two types of system. It is also useful to note that under the definition given, self-micro emulsifying drug delivery system are not micro emulsions, although they may be considered to be a closely related system. typically comprises a mixture of surfactant, oil and drug (known as the concentrate)which when. introduced into the body is rapidly dispersed to form droplets of approximately the same size range as those observed in micro emulsion systems. Once dispersed such systems would be expected to be have in vivo much the same way oil-in-water (o/w) micro emulsions. Conventional surfactant molecules comprise a polar head group region and anapolartail region, the latter having the larger molecular volume particularly in the case of ionic surfactants. On dispersal in water, surfactants self-associate into a variety of equilibrium phases, the nature of which stems directly from the interplay of the various inter and inter- molecular forces as well as entropy considerations. Surfactants also self-associate in non-aqueous solvents, particularly a polar liquids such as alkanes.

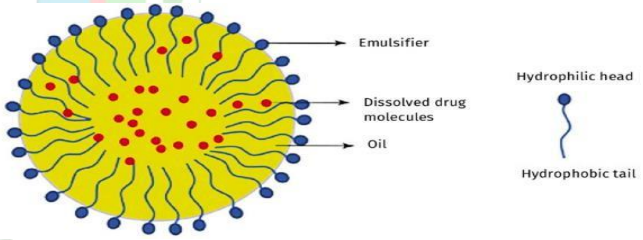


Figure 2: Structure of Microemulsion

In this case the orientation of the surfactant molecules is reversed compared to those adopted in aqueous solution.[21]This reorientation serves to optimize the solvation requirements of the surfactant and mini- mises the free energy of the system overall. When surfactants are incorporated into immiscible mixture esofoil and water, the surfactant molecules can locate at the oil/water interface which is thermodynamically very favorable. A number of phases can result which may be structured on the microscopic or macroscopic scale, one example of a phase structured on the microscopic scale is an optically iso-tropic microemulsion phase. The schematic given in gives an indication of a few of the wide variety of possible self- associations tructures That surfactants can formin the presence of water,oil or Combinations of all three. Although outside the scope of this Review many of the structures shown in, as well as some of those Not shown, have potential for use as drug delivery systems.[22] It Can be seen while the three structures shown are quite different, In each there is an interfacial surfactant monolayer separating the Oil and water domains.

Materials and Methods

Cefotaxime was purchased from yarrow chem product Mumbai, India. Other chemicals such as, oleic acid, castor oil, polyethylene glycol 600, propylene glycol, tween 80, span 80, were supplied by S. D. Fine Chemicals, Mumbai.

Selection of the Oil Phase

The oil phase was selected based on the drug's solubility profile. Various oils, including castor oil, oleic acid, peppermint oil, iso propyl myristate, were evaluated through solubility studies. Among the tested oils, oleic acid exhibited the highest solubility for the drug and was therefore chosen as the oil phase for the formulation.[23]

Selection of Surfactants and Co-surfactants

The solubility of Cefotaximewas assessed in various surfactants and co-surfactants. Additionally, the emulsification efficiency of these components was evaluated to determine their capacity to emulsify the selected oil phase.

Determination of Percent Drug Solubility

To assess emulsification ability, an equal proportion of surfactant was mixed with the drug, diluted appropriately, and the resulting solution was analyzed for transmittance at 233 nm using a UV-Visible spectrophotometer. The formation of a uniform emulsion was further evaluated based on the number of flask inversions required to achieve homogeneity. Co-surfactants were similarly screened, with selection based on their ability to form stable, transparent microemulsions at minimal concentrations.[24]

Solubility study

About 1ml of oil was accurately weighed in 10 ml Glass beaker and add Cefotaxime drug, followed by stirring on magnetic stirrer at moderate Speed to dissolve the drug and sonicate it for proper dissolution. Addition of drug was Continued until the supersaturated solution is obtained. Finally, the total amount of drug consumed was Determined by using UV Spectrophotometer at 233 nm. In the similar way solubility of Cefotaxime was Checked in different surfactants and co-surfactants and oils.[25]

Table 1: % Drug Solubility

Surfactants	**Excipients**	**Percent Drug**
	Tween 80	90.38
	Tween 20	53.12
	Span 80	76.40
	Span 40	79
Oils	Excipients	Percent Drug
	Peppermint oil	64.46
	Castor oil	66.76
	Oleic acid	91.82
	Iso propyl Myristate	85
Co surfactants	Excipients	Percent Drug
	Ethanol	79.40
	Polyethylene glycol	65.27
	Propylene glycol	92.36
	Polyethylene glycol 600	74.88

Construction of Pseudo-Ternary Phase Diagrams

The pseudo-ternary phase diagrams were constructed Using water titration method to determine the Microemulsion area and to detect the possibility of Making microemulsions with different possible Compositions of oil, surfactant/co-surfactant and water Respectively. The ratios of surfactant to co-surfactants and co-emulsifier Were selected to be 1:1:0.25, 1:2:0.25, 2:1:0.25, 1:3:0.25, and 3:1:0.25. These mixtures (S/Cos) were mixed with the Oil phase to give the weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9. Water was added drop by Drop and stirred using a magnetic stirrer at constant Temperature. After each addition, the system was Examined for the physical appearance. The end point of the titration was the point where the solution becomes Transparent or translucent. The amount of the aqueous Phase required to make the mixture turbid was noted. The percentages of the various incorporated pseudo-Phases were estimated, and the same procedure was Followed for the other S/Cos ratios. All the ratios of S/Co give dotted area in pseudo ternary phase Diagram.[26][27] phase diagram was constructed using CHEMIX software.

Preparation of drug loaded Microemulsion

Based on the phase diagram, the optimum Smix ratio was selected and the drug loaded microemulsion were prepared by dissolving the drug in the oil-Smix mixture, and then titrated with water on the magnetic stirrer at 150 RPM for 10 min. Cefotaxime was added to the specific amount oil then surfactant and co-surfactant with varying percentage, and then an appropriate amount of water was added to the mixture drop by drop with constant stirring on magnetic stirrer. Microemulsions containing Cefotaxime were obtained spontaneously on stirring the mixtures. All microemulsions were stored at appropriate temperature. Four formulations containing different concentration of oil, Surfactant/co-surfactant were prepared with the help of selected region area of pseudo ternary phase diagram. The higher microemulsion region shown in phase that ratio is selected for formulation process. Each formulation was prepared according to the procedure explained above and then these formulations were evaluated.[28][29]

EVALUATION OF MICROEMULSION

pH determination

The apparent pH of all microemulsion formulations Was determined at 25°C by immersing the electrode Directly into the microemulsion formulations using a Digital pH meter.[30]

Phase Separation

Microemulsion systems were subjected to centrifugation at 3000 rpm for a period of 2 h and examined for any evidence of phase separation.

Viscosity measurement

Microemulsion are generally low viscosity systems. The viscosity of the prepared microemulsion was Measured at 37°C at 60 rpm by LV 2 spindle no. 63 Using a Brookfield viscometer.[31]

Determination of Drug Content

The drug content of the microemulsion formulations was determined by dissolving 0.1 ml (equivalent to 225 Mg drug) of the formulation in 10 ml of methanolic phosphate buffer. After suitable dilutions with methanolic phosphate buffer, absorbance was determined using the UV spectrophotometer keeping Blank solution as methanolic phosphate buffer as control at wavelength 233 nm and three replicates were performed for each sample.[32]

Measurement of Particle Size

The average globule size of the microemulsions was determined by Zetasizer Nano-ZS (Malvern Instruments, UK). Measurements were carried at an angle of 90◦ at 25◦. Microemulsion was diluted with double distilled water to ensure that the light scattering intensity was within the instrument's sensitivity range. All the measurement was carried out at 25˚. The polydispersity index of the formulation was determined by the same instrument. The width of the size distribution was indicated by the polydispersity index.[33]

Measurement of zeta potential

The zeta potential was determined to verify stability of microemulsion due to charge interaction. Zeta potential was measured by using Zetasizer Nano-ZS (Malvern Instruments, UK). The measurement was performed at 25°.

In vitro Drug release

In vitro diffusion was carried out by modified franz diffusion Cell. A glass cylinder with both ends open, 10 cm height, 2.7 Cm outer diameter and 1.5 cm inner diameter was used as Diffusion cell. A sheep nasal mucosa was fixed to one end of the cylinder with the aid of an to result as a diffusion cell. 1 Ml of microemulsion was taken in the cell (donor Compartment) and cell was immersed in a receptor cell containing 20 ml of pH 6.8 Phosphate buffer as receptor compartment. The entire surface of the cell was in contact with the receptor Compartment which was agitated using magnetic stirrer and A temperature of 37±1° was maintained. Samples 20 ml of the receptor compartment were taken and with same Amount replaced to maintain sink condition. The sample was Analysed for Cefotaxime at 233 nm against blank using UV Spectrophotometer. Amount of Cefotaxime released at Various time intervals was calculated with the help of Calibration curve with phosphate buffer and plotted against Time.

RESULTS AND DISCUSSION

Construction of Pseudo-Ternary Phase Diagram

From these pseudo ternary phase diagrams, the microemulsion region was identified and it was found that within each Microemulsion region, the solution of the microemulsion was transparent and was with a low viscosity. No distinct Conversion from oil in water to water in oil microemulsion Was seen. Therefore, this single isotropic region was a biscontinuous microemulsion. The rest of the region in the t-phase diagram shows either a turbid solution of microemulsion or the gel form of the mixture. Oleic acid/Tween 80/propylene glycol system in case of oleic acid, the microemulsion region was decreased with an increase in the gel area. During the water titration method of oleic acid, it was found that oil and the Smix itself forms a very thick mixture and addition of water turns it to the gel. The Phase changes were increased as the concentration of the oil Was increased. In this case also, three phase diagrams were Studied with a change in the concentration of the emulsifier (Tween 80) and the constant concentration of the co-emulsifier 0.25 (1:1, 1:2, 2:1, 1:3, 3:1, w/w). From these, the phase diagram having the largest area of the microemulsion was selected. It was found that the phase Diagram with a composition of emulsifier (Tween 80) and Co-emulsifier (propylene glycol) 1:3 w/w had the maximum area of microemulsion and hence was selected as the best composition for the microemulsion. It was possible to incorporate a maximum of 10 ml of oil into the microemulsion when the Smix in the ratio of 1:3 w/w was used. This ratio is used for future study.

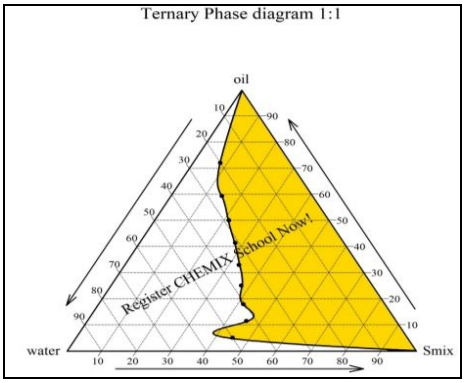
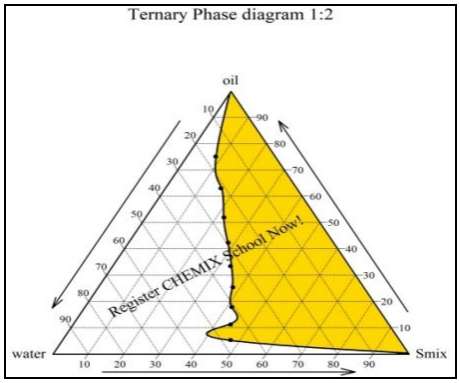


Figure: 3



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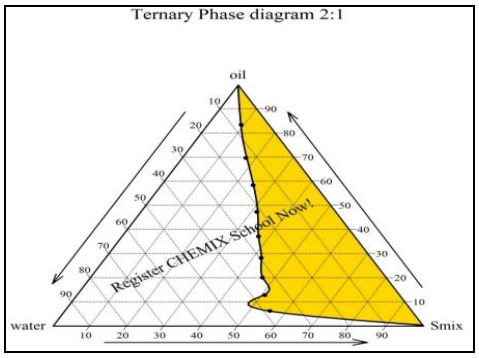

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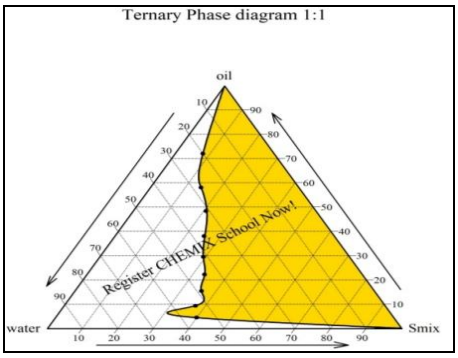

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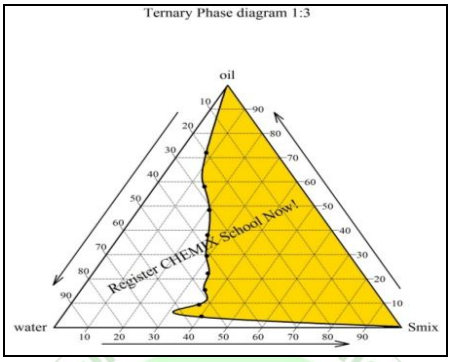

Figure: 7

pH Determination

The pH of various Microemulsions is shown. Which was found to be in range of 4.6 to 6.2? Nasel irritation is minimised when product is delivered. With a Range of 4.5 to 6.5

Table 2: pH Determination

Batch no.	Result
F1	6.2
F2	4.6
F3	5.6
F4	5.2

Phase Separation

Microemulsion systems were subjected to centrifugation at 3500 RPM for a period of 1 h and results is shown in following table.

Table 3: Phase Separation

Batch no	Result
F1	No Phase separation
F2	No Phase separation
F3	No Phase separation
F4	No Phase separation

Viscosity Measurement

The viscosity of all the formulation of microemulsion was measured using a Brookfield rotational viscometer (LV2, Brookfield) at 37°C at 10, 20, 30, 40; 50 RPM formulation with higher viscosity has a better contact time thus increase the absorption. high viscosity enhanced the permeability of drug.

Drug Content

The results of % drug content are shown in table no 18 batch shows the least Drug Content about 70.57% and higher drug content was shown by F3 batch 83.95. shows the comparison of % Drug Content of formulations F1 to F4

Table 4: % Drug Content

Sr no	Batch no	Drug content
1]	F1	80.4
2]	F2	70.57
3]	F3	83.95
4]	F4	78.62

In the drug content study, the drug content was calculated and observations were made as for formulation, F1= 80.4 %, F2= 70.57 %, F3= 83.95% , F4= 78.62% , respectively. It can be concluded that F3 batch show more Drug content.

Particle Size

Average particle size of Solid lipid Nanoparticles was determined by MALVARN ZETASIZER

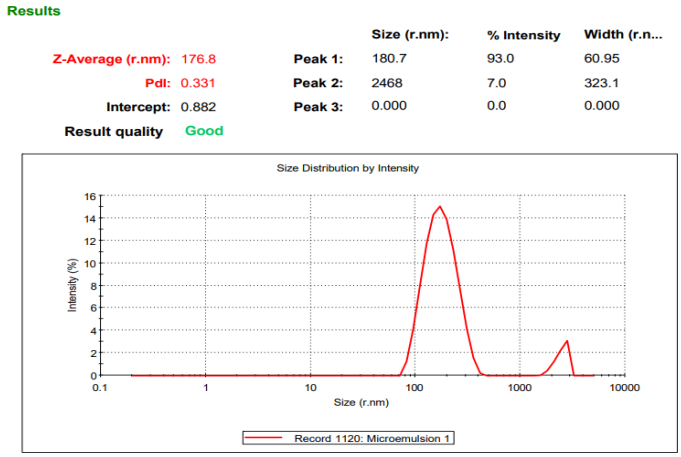

Figure 8: Particle Size

This graph illustrate the distribution of particle sizes within a sample. The x-axis represents the size of particles, typically ranging from nanometers to micrometers, while the y-axis shows the frequency or proportion of particles within each size range. The average particle size of optimize formulation F4 was found to be 176.8 nm**.**

Zeta potential

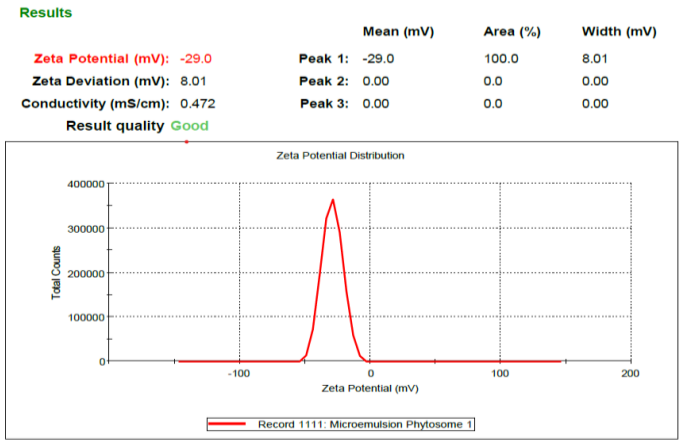

Figure 9: Zeta potential

Zeta potential of the microemulsion was determined by MalvarnZetasizer, illustrate Zeta potential for optimized batch of Microemulsion was -29.0 mV indicating presence of optimum charge on the surface of formulations to prevent aggregation during their shelf life.

In vitro drug release

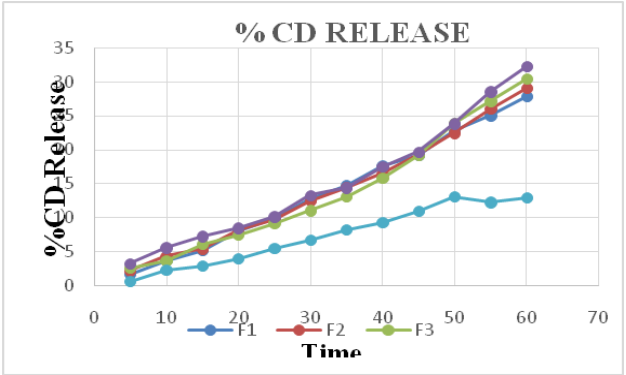

Figure 10: In-vitro drug release

Table 5: Regression Coefficient of F4

Regression Coefficient of (R^2) values				
Sr no	**Zero order kinetics**	**First order kinetics**	**Higuchi Model**	**Korsmeyer Peppas**
1.	0.9644	0.9445	0.8972	0.9803

CONCLUSION

Microemulsions present a promising drug delivery system for phytoconstituents of Cefotaxime, a widely used antibacterial agent. This formulation typically consists of oil, a surfactant mixture (Smix), and the drug component. Microemulsions offer several advantages, such as enhanced drug stability, improved bioavailability of poorly soluble drugs, and controlled release kinetics. The lipid layer within the microemulsion protects the drug from degradation and enables sustained release, resulting in better therapeutic efficacy and fewer side effects.In this study, Cefotaxime-loaded microemulsions were developed for nasal delivery, targeting the treatment of meningitis. Prior to incorporation into delivery systems, the microemulsions were evaluated using various analytical parameters, including FTIR spectroscopy, drug content analysis, particle size measurement, and in-vitro diffusion studies. The optimized formulation was then filled into vials and subjected to further evaluation.A stability study was conducted over ten days at different temperatures. The formulation's drug entrapment efficiency and physical appearance were assessed, revealing that the microemulsion remained more stable at room temperature compared to elevated temperatures (40°C).

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