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DEVELOPMENT AND COMPARISON OF CEFIXIME NANO EMULSIONS WITH SOME OF THE CEFIXIME FORMULATIONS AVAILABLE IN INDIAN MARKET

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ABSTRACT
The primary intention of this research was to progress and assess a Nano emulsion (NE) formulation of cefixime with the goal of enhancing its oral bioavailability. The formulation of the cefixime NE utilized a compilation of homogenization and sonication methods. Through comprehensive FTIR studies, the affinity of the drug and its excipients was confirmed. Characterization of the augmented Cefixime NE elaborate a sequence of analyses counting Particle size (PS) determination, assessment via Differential Scanning Calorimetry (DSC), evaluation of Zeta Potential (ZP), drug content measurement, and in-vitro drug release studies. To assess its antimicrobial activity, the cefixime Nano emulsion was subjected to testing using the Disc plate proceeding counter to Escherichia coli (E. coli) strains, with varying concentrations of the created groundwork, tested on nutrient agar. The Minimum Inhibitory Concentration (MIC) was determined liable the calculation of Zone of inhibition.

KEYWORDS: Nano emulsions, Cefixime, Bioavailability, Zeta potential, Homogenization, Sonication.

INTRODUCTION

Nano emulsions and Nanotechnology

Nano emulsions represent a nano sized particulate matter system characterized by submicron-sized particles, serving as effective carriers for drug particles. Their sizes grades from 10 - 1,000 nanometres. These carriers consist of solid spheres with amorphous, lipophilic surfaces bearing a negative charge. Nanoparticles offer enhanced site specificity.[1] As a drug delivery system, they improve the therapeutic effectiveness of medications while minimizing adverse effects and toxic reactions. An emulsion is a two-phase system where one phase is distributed within the additional in the system of tiny droplets, typically ranging from 0.1 to 100 micrometres in diameter.[2] This system is thermodynamically unstable but can be alleviated by the incidence of an emulsifying agent, also acknowledged as an emulgent or emulsifier. The distributed phase is mentioned to as the discontinuous phase, whereas the superficial phase is acknowledged as the dispersion medium, external phase, or constant phase. The emulsifying agent, also termed intermediate or interphase, be given a paramount importance in even out the emulsion.[3] The term "nanoemulsion" denotes a fine dispersion of oil in water or water in oil, alleviated by a surfactant molecule forming an interfacial film, with droplets typically ranging in size from 20 - 600 nanometres. Due to their small size, nanoemulsion exhibit transparency.[4]

Method of preparation

NE are equipped using various methods, therein be broadly classified into low-energy or high-energy emulsification approaches, or a grouping of both. High-energy methods involve systemic tool that generate influential unsettling forces to interrupt the organic and aqueous phases and form oil droplets. These techniques employ high-pressure homogenizers, microfluidizers, and sonication methods. In disparity, low-energy techniques utilize the intrinsic synthetic vitality of the organization for emulsification.[5] This is achieved by harnessing the chemical physical properties of the surfactant, co-surfactants, and excipients within the formulation. Cefixime is a tertiary-peer group cephalosporin antibiotic with low solubility and absorptivity. Its bioavailability is limited, typically ranging from 30% to 40%. Affordable formulations are sought to enhance bioavailability and drug delivery. The intention of this study was to advance a stable nanoemulsion preparation of cefixime to improve its solubility, stability, and oral bioavailability.[6]

Cefixime, belonging to the third generation of cephalosporin antibiotics, is used for various infections such as pharyngitis, otitis media, gonorrhea, bronchitis, and urinary tract infections.[7]

Antibiotics

Antibiotics are chemical substances produced by living organisms, typically microorganisms, to combat other microorganisms. They are commonly derived from soil microorganisms and serve as a means of controlling the growth of competing microorganisms in complex environments like soil.[8] Notable antibiotic-producing microorganisms include bacteria and fungi. The period of antibiotics began with the ascertain of penicillin in 1941, marking a significant advancement in the dealing of bacterial infections in both humans and animals.[9] Despite their effectiveness, antibiotics are ineffectual alongside viruses. The use and administration of antibiotics are governed by principles aimed at ensuring effective treatment while minimizing side effects.[10] It is essential to administer antibiotics to patients to which the target bacterium is sensitive, at a concentration sufficient for efficacy but without causing adverse effects, and for a duration necessary to eradicate the infection completely. Antibiotics vary in their spectrum of action, with some being highly specific and others broad-spectrum, capable of combating various bacteria, including mixed infections.[11]

Antibiotics are classified as per their spectrum of activity, categorized as narrow-, broad-, or extended-spectrum agents. Narrow-spectrum antibiotics primarily target gram-positive bacteria, while broad-spectrum antibiotics affect both gram-positive and some gram-negative bacteria. Extended-spectrum antibiotics, resulting from chemical modifications, target additional types of bacteria, often gram-negative ones.[12]

Diverse sorts of antibiotics operate in unique ways. Bactericidal antibiotics, like penicillin, slay bacteria via interfering with the formation of the bacterial cell wall or its cell contents. On the other hand, bacteriostatic antibiotics inhibit bacterial multiplication, allowing the body's immune system to eradicate the infection gradually. It abducts sometime after starting antibiotic treatment for patients to experience symptom relief or improvement.[13]

Materials

Polyoxyethylene Castor oil is a general term encompassing various PEGylated Castor oil byproducts obtained by countering Castor oil with varying amounts of ethylene oxide. Each derivative is designated with a numerical suffix (X), indicating the quantity of ethylene oxide equivalents added to one Castor oil equivalent.[14] As non-ionic surfactants, Polyoxyethylene Castor oils find widespread use in pharmaceutical formulations, fragrance products, hair sprays, deodorants, and indoor tanning preparations.[15]

These derivatives consist of complex mixtures, akin to natural glycerides, comprising primarily Polyethylene glycol conjugates, fatty acid esters of Polyethylene glycol, and ethoxylated glycerol.[16] Ethoxylation occurs through both etherification of free alcohol groups and transesterification, resulting in the insertion of Polyethylene glycol groups between glyceryl and fatty acid components.[17] Moreover, some ethylene oxide molecules react with others, leaving some Polyethylene glycols unattached. Hence, Hydrogenated Castor oil triglycerides constitute intricate blends of structurally related molecules.[18]

Method validation

Method validation is an integral section of the validation process, ensuring through laboratory studies that the method's performance characteristics align with the necessities aimed at its intended analytical application.[19] Technique expansion and authentication are intertwined, with validation confirming the efficacy of the developed method and its performance parameters. The necessity for validation in analytical laboratories is underscored by regulatory guidelines such as those established by the International Conference on Harmonization (ICH), Current Good Manufacturing Practices (cGMP), Good Laboratory Practices (GLP), and Good Clinical Practices (GCP).[20] Validation parameters encompass various aspects including Identification, Linearity, Precision, Specificity, and Recovery, collectively ensuring the robustness and dependability of the investigative method.[21]

Determination of absorption maxima by using UV Spectrophotometer

The estimation of the maximum absorbance of Cefixime involved the groundwork of a standard solution by dissolving 100mg of Cefixime in a 100mL volumetric flask with 50mL of methanol, followed by dilution with 0.1N HCl to the mark. From this stock solution, a standard stock solution of 100µg/ml concentration was prepared by further dilution with 0.1N HCl. The absorbance of this standard stock solution was then scanned between 200-800nm to define the maximum absorbance.[22]

Solubility studies

Take 1gm of solute liquefy in the solvent of choice in a beaker. Mix the solution for definite timespan & permit the solution to reach equilibrium. Carry out the equivalent procedure for other available solvents and find out the suitable solvent for the solute grounded on the derived results. Furtherly, the concentration of the separate solution can be determined.

For choosing the suitable better solvent for cefixime solubility dissimilar solvents were measured and tabulated as follows

Table 1: Solubility profile of Cefixime in different solvents.

Solvents	Solubility
Water	Insoluble
Ethanol	Partially soluble
Methanol	Freely soluble
Acetone	Partially soluble
Propylene Glycol	Freely soluble
Ethyl Acetate	Insoluble
Hexane	Insoluble
Ether	Insoluble

From the above tabulated detailed literature survey, we came to the conclusion that methanol suited to the most extent can be used as the solvent for cefixime better solubility.[23]

Compatibility studies

Compatibility studies were conducted using DSC and Fourier-transform infrared (FTIR) spectroscopy. DSC analysis was executed using a Venchal Scientific DSC instrument. The procedure for the DSC analysis includes: Possess the sealed pan in the sample tray. Mark the slot number. Keep the reference pan in a reference slot. The reference pan is an unoccupied sealed pan. Keep the reference pan so that numerous runs can be performed with it. Switch on the control to the cooler. Open the software. TA common examination on the desktop of the computer. Now twitch the cooler. The temperature of the cell is shown in the status bar. Set upon the nitrogen air tank with pressure held should be 20 psi and illustration purge flow must be 50 ml/min. On the programme in the centre panel termed subsequently the information for the illustration that it is running. You want to seal out all the information. Click on the test to alter the process category. Then set the temperature, holding time. Note that functioning assortment of equipment is 80^0 C to 400^0C.

FTIR studies were conducted to detect possible interactions between Cefixime and excipients used in the nanoemulsion formulation.[24] FTIR studies were accepted out by using the Bruker's Alpha-E model instrument. The procedure for the analysis includes: Firstly, the sample is positioned in a container in the pathway of the IR source. A sensor orates the analogue signal and converts the signals and identify the peaks. An IR stream of light drives over a partly silvered looking glass, that ripping the ray into equal halves and give the desired results.

A standard calibration curve for Cefixime was established by preparing a primary stock solution of 100mg in a 100mL volumetric flask, followed by dilution to 100µg/ml concentration. Dilutions oscillating from 2 to 12µg/mL were prepared from this secondary stock solution, and the absorbance was measured using a UV spectrophotometer. The λmax was originate to be 287nm, with a Beer's range of 2-20mg/mL.[25]

Formulation details

The research of Cefixime nanoemulsion involved dissolving 100micro gram of Cefixime in 10 mL of methanol, followed by the addition of castor oil, PEG 400, and Tween 80, and making up and about the capacity to 100mL with water. The mixture was then subjected to homogenization for 1 hr at 8000rpm, followed by further treatment with a magnetic stirrer and sonication for 6 minutes with intervals.[26]

Table 2: Formulation table of the prepared Nano emulsion.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm
Castor Oil	5ml	15ml	10ml	20ml	10ml	5ml	8ml	10ml	25ml
Tween 80	8ml	25ml	20ml	15ml	10ml	15ml	5ml	10ml	13ml
PEG 400	5ml	5ml	10ml	15ml	20ml	10ml	15ml	10ml	7ml
Methanol	5ml	15ml	10ml	20ml	25ml	5ml	12ml	10ml	15ml
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

From the above formulation table and the attained results, it can be resolved that the F3 formulation with the sufficient values yielded good results compared with other formulations.

RESULTS AND DISCUSSIONS

Evaluation parameters for cefixime nanoemulsion

1. **Particle size analysis:** Particle size analysis was carried out by using Nano particle size analyser. The average particle size (PS) of cefixime nanoemulsion formulations was determined using the Horiba Scientific SZ-100 instrument.[27] The procedure for the analysis is as follows:

Check it out the surroundings if it is not clean. Clean it properly switch on the main. Switch on the instrument. Open the software Wizard. Switch on the instrument main switch main switch wait for5min. Then switch on laser lamp and temperature panel cell. Set temperature

shows in yellow colour. Cell temperature is controlled shows in blue colour. The data is processed using an external program. To open the programme, click TA Universal analysis on the desktop. Open the file for the model being processed. When the file is released all the documents together is offered. If the database used comprises numerous loops you will need to choose the appropriate cycle to analyse. This is done by going to edit tab. Clicking cycle list then select the particular cycle. The suitable analysis type has been carefully chosen (i.e., glass transition, melting temperature. etc.). This is done under analyse lab. Once the investigation type has been selected. Two signs will be displayed on the data. The marks need to be snapped and pulled thus that one is on each sideways of the transition state. Following, left click and select accept limits. The temperature for the beginning, middle, and end of the transition will seem on the screen. To distribute the data to be additional administered in excel, mat lab…etc. go to file. Transfer data file. File and plot signals. Spreadsheet text file. Click finish, title the folder, and tick save.

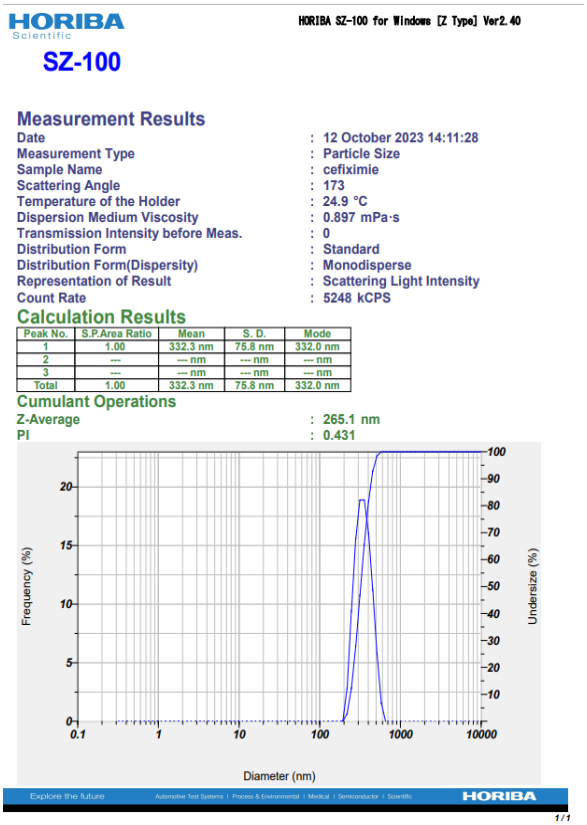

Fig. 1: Particle size graph of the Homogenized sample.

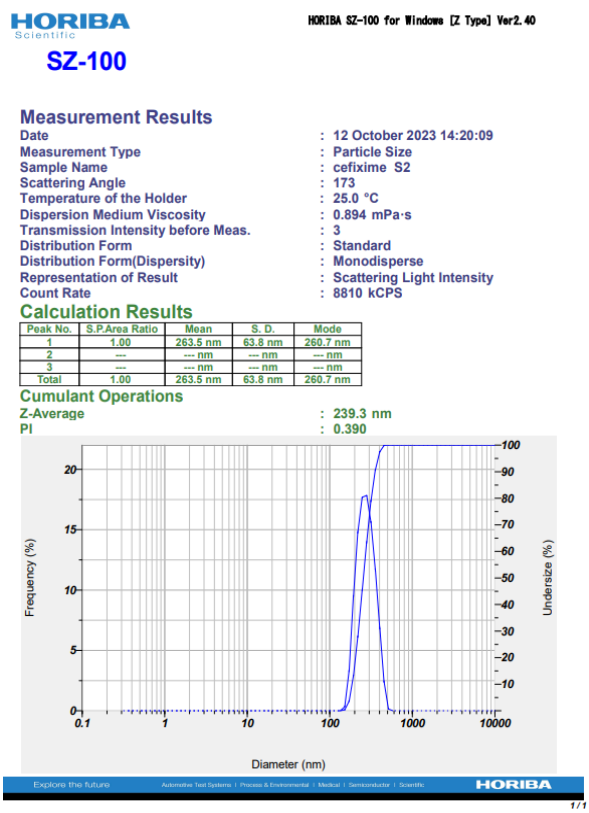

Fig. 2: Particle size of the Sonicated sample.

The determined particle size of the prepared Nano emulsion of the homogenized and sonicated samples were performed and was discovered to be 261.5 and 239.3 nm respectively.

2. **Polydispersity Index (PDI):** The mean polydispersity index (PDI) was measured directly using the Horiba Scientific instrument. PDI values for all nanoemulsion formulations were ensured to be less than 0.8(28).

3. **Zeta Potential:** ZP measurements were conducted using Horiba Scientific SZ-100 instrument to evaluate the electric charges at the surface of the particles. This parameter indicates the physical stability of colloidal systems by determining the electrophoretic mobility of the particles.[29]

4. **Drug content:** The drug content of cefixime Nano emulsion was performed by dissolving 100mg of cefixime in 100mL of 0.1N HCl in a volumetric flask. A portion of this solution was extracted, thinned, and analysed using a UV Spectrophotometer at a wavelength of 287nm.[30]

5. **In-Vitro drug release studies:** Drug release studies were conducted in phosphate buffer solution (PBS) with a pH of 7.4 as the medium. Cefixime Nano emulsion models were situated in a dialysis casing knotted to the aperture of a measuring cylinder, which was inverted over a beaker containing PBS. The system was then agitated at 50 rpm and 37±0.5°C. At fixed time breaks, samples were extracted, sifted, and analysed using a UV Spectrophotometer at a wavelength of 287nm (31).

6. **Antimicrobial studies:** Nutrient agar was equipped by dissolving 1.05 g in 50 mL of distilled water, autoclaved, and allowed to solidify. E. coli was inoculated onto the agar plates, and 10mm disks were placed. After incubation (ZI) at 35°C for 24 hours, the ZI was measured to calculated the antimicrobial activity of the cefixime nanoemulsion (32).

Comparative study of antimicrobial activity of marketed Products and Cefixime nano emulsion

Zone of Inhibition (ZOI) is a vibrant spherical zone round antimicrobial discs in which microbes are incapable to produce. Zone of Inhibition challenging is a fast, qualitative means to measure the capability of an antimicrobial agent to hinder the progress of microbes. In the present study, the zone of inhibition of the screened Nano emulsion formulation of Cefixime was measured and then compared with different marketed products. The pure cefixime drug was also added in the comparison along with the homogenized and sonicated cefixime nano emulsion preparations. The results are shown in Table. It was observed that the zone of inhibition of Cefixime nano-emulsion formulation was more compared to the other marketed products. As this was observed owing to the subdued particle size of the nano emulsion preparation that enhanced drug properties to show the required therapeutic activity in a greater scale compared with other marketed products. The zone of inhibition of the antimicrobial agents was achieved using different strains of the microorganisms.

Table: Zone of Inhibition of Cefixime nano emulsion and other marketed products for different strains

Zone of Inhibition (mm)

Table 3: Zone of Inhibition measures of the arranged formulation on different strains.

Sample	E.coli	P.aureginosa
Type 1	16	18
Type 2	14	14
Type 3	20	23
Type 4	23	25
Type 5	28	28
Pure form of Cefixime	35	40
Homogenized Cefixime sample	30	35
Sonicated Cefixime sample	30	35

Compatibility studies

1. Standard calibration curve

The absorbance maxima of cefixime were observed at 287nm, demonstrating excellent linearity (r2 = 0.9991) across the concentration series of 2 to 12µg/ml, adhering to Beer-Lambert's law. The linear equation was determined as y = 0.0512x - 0.0039 with R^2=0.9991.

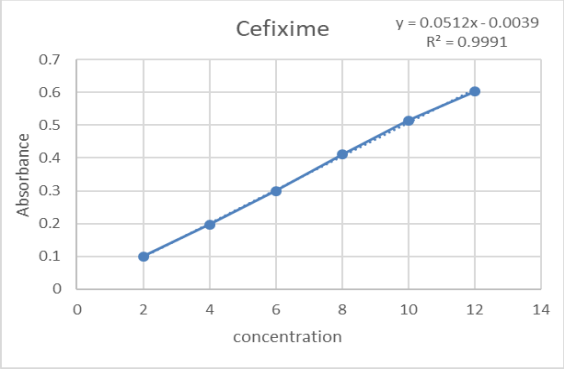

Fig. 3: Standard calibration curve graph of cefixime.

2. **FTIR Spectroscopy:** FTIR spectra of pure cefixime, physical mixtures containing excipients, and cefixime nanoemulsion were analysed. Similar peaks of functional groups were observed in all spectra, indicating no interaction between the drug and polymers.

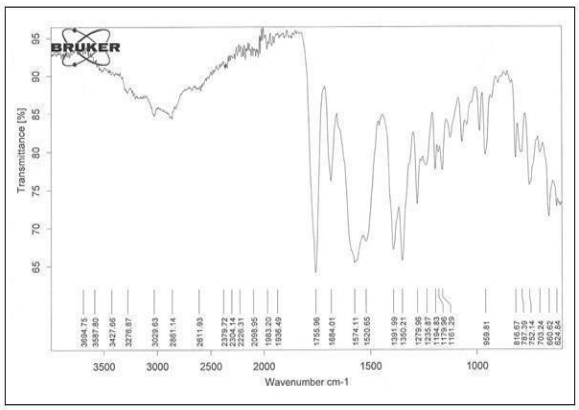

Fig. 4: FTIR Spectra of the Cefixime sample.

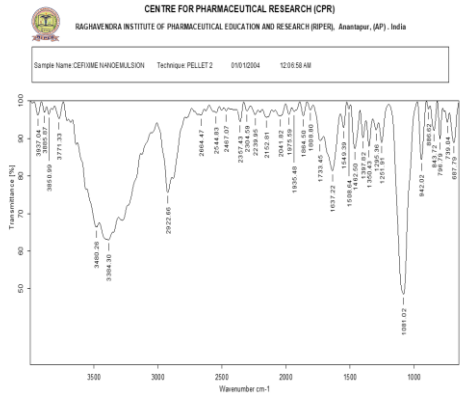

Fig. 5: FTIR spectra of the Cefixime Nano emulsion.

3. DSC: The melting point of pure API cefixime ranged between 218-225°C, with a smooth, blunt peak observed at 202.0°C. Similarly, cefixime nanoemulsion exhibited a peak at 128.0°C.

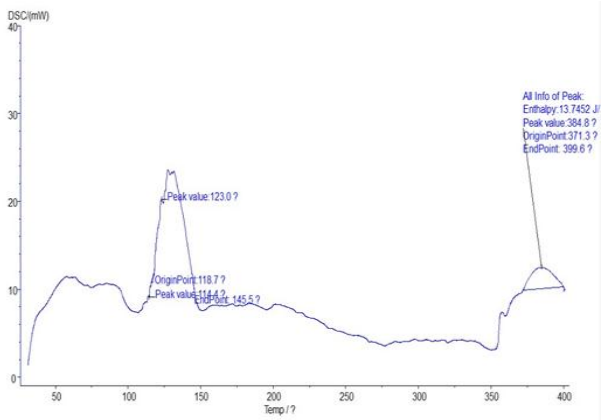

Fig. 6: DSC Thermogram of the prepared Nano emulsion.

4. Antimicrobial studies: The antimicrobial activity of cefixime nanoemulsion against E. coli was evaluated using the disk plate method. After completion of the test, the ZI was measured, and images were captured to visualize the results.

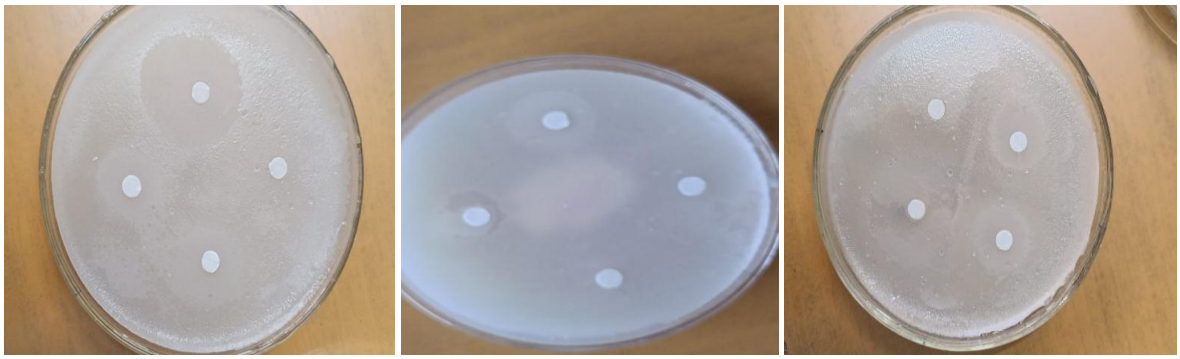

Fig. 7: Zone of Inhibition measured for the pure cefixime, homogenized, sonicated, marketed formulations in each disc plate.

CONCLUSION

The current study work has been acceptable and well-organized accomplishment and a try to formulate cefixime Nano emulsion prepared by using High energy approaches like Homogenization and furtherly followed by Probe Sonicator. The use of wetting agent and excipients like castor oil, Tween 80, PEG 400 has been compatible with the drug and its formulation as resolved on by compatibility studies like FTIR and DSC. Enhancement in the concentration in the surfactant enhances the particle size and enhancement in the polymer concentration enhances the drug content and particle size. Cefixime Nano emulsion along with excipients was detected as unchanging and exhibited particle sizes in series and a good proportion yield than articulating alone. The comparative microbiological

studies performed concluded that the zone of inhibition of the prepared Nano emulsion was more compared to others. Therefore, it can be concluded that Cefixime Nano emulsion prepared using Homogenization and probe sonication technique offer an easy, time saving and efficient method than other conventional methods. It can be also decided that cefixime formulated as a Nano suspension dosage form is orally active with increased bioavailability than the drug alone.

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