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Research Article

**PREPARATION AND EVALUATION OF SUSTAINED  
RELEASE MICRO EMULSION OF CEFPODOXIME  
PROXETIL****Dolly Gupta\*<sup>1</sup>, Yamini Shah<sup>2</sup> and Dushyant Shah<sup>1</sup>**<sup>1</sup> A.P.M.C College of Pharmacy, Himmatnagar, Gujarat, India.<sup>2</sup> L.M College of Pharmacy, Ahmedabad, Gujarat, India.**Abstract:**

*Now a day oral route is the easiest and most prominent route for drug delivery. More than 40% of new chemical entities exhibit poor aqueous solubility result in unsatisfactory oral drug delivery. Cefpodoxime Proxetil is a Class IV drug, possess lower solubility and lower bioavailability. The aim of this study was to formulate and evaluate a Micro emulsion to overcome these issues. Capmul MCM was selected as an oily phase, tween 80 as a surfactant and PEG 400 as a co-surfactant. The batches of emulsion were formulated by spontaneous emulsification method. Different concentrations of Surfactant and Co. Surfactant were used to formulate micro emulsion. Evaluation parameters such as Globule size, pH, Viscosity, Clarity, Dilution test, Centrifugation and Freeze Thaw method were tested. %CDR, Drug content and Anti-microbial assay were also calculated.*

**Keywords:** Micro Emulsion, Cefpodoxime Proxetil, Globule size, Freeze Thaw, Anti-microbial.**Corresponding author:****Dolly Gupta**

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**INTRODUCTION:**

Oral route still remains the favorite route of drug administration in many diseases. Even today it is the most preferred route in the development of new dosage forms. Successful oral delivery of drugs has always remained a challenge to the drug delivery field, because approximately 40% of the new drug candidates show poor water solubility, thus oral delivery is frequently associated with implications of low bioavailability [1]. In recent years, much attention has been focused on lipid based formulations to improve the oral bioavailability of poorly water soluble drug compounds. In fact, one of the most popular approaches is the incorporation of the active lipophilic component into inert lipid vehicles such as oils, surfactant dispersions, nano emulsions, micro emulsions, self-emulsifying formulations, self-Nano or micro emulsifying formulations, emulsions and liposomes [2].

Micro emulsion a novel drug delivery system has been reported to improve the rate and extent of absorption of lipophilic drugs [3]. Hoar and Schulman stimulated the interest of researchers in micro emulsion in 1943 when they found that the addition of a strong surface-active agent resulted in emulsions of oil and water without vigorous shaking [4]. Micro emulsions are clear, transparent, optically isotropic and thermodynamically stable systems comprising of oil, surfactant, co-surfactant and aqueous phase [5]. Nano emulsions are thermodynamically stable transparent [translucent] dispersions of oil and water stabilized by an interfacial film of surfactant and co surfactant molecules having a droplet size of less than 100 nm [6].

Although there is similarity between emulsion and micro emulsion, the latter vary in that the average drop size does not grow with time like conventional emulsion due to thermodynamic stability [7]. The clear appearance of micro emulsion is another difference in comparison to the emulsion which is turbid [8]. An additional difference is in the shape of the particles dispersed in the continuous phase; emulsions consist of roughly spherical droplets of one phase dispersed into the other while micro emulsions constantly evolve between various structures ranging from droplet-like swollen micelles to bi-continuous structures [9, 10].

Cefpodoxime Proxetil [1-[[isopropoxycarbonyl]oxy] ethyl ester of [Z]-7-[2-[2-amino-1, 3-thiazol-4-yl]-2-methoxyiminoacetamido]-3-methoxymethyl-3- cephem-4-carboxylic acid] is the orally active ester pro-drug of third generation Cephalosporin [11]. Cefpodoxime Proxetil is an orally absorbed, broad spectrum, third-generation cephalosporin ester implicated in treatment of upper respiratory tract and urinary tract infections [12]. Although Cefpodoxime Proxetil, the pro-drug

ester, is hydrolyzed in vivo to its active metabolite, Cefpodoxime is designed to improve the permeability and thus bioavailability of the parent molecule Cefpodoxime Acid; it still has only 50% oral bioavailability when administered orally [13]. Cefpodoxime Proxetil is a non-crystalline, slightly basic compound and is absorbed from the gastrointestinal tract after oral administration and hydrolyzed to its parent moiety Cefpodoxime Acid by nonspecific esterase in the intestinal wall/plasma [14]. The reasons for low oral bioavailability of Cefpodoxime Proxetil are mainly attributed to low water solubility [400 µg/ ml] and pre-absorption luminal metabolism of its ester side chain by digestive enzymes cholinesterase present in the intestinal lumen into Cefpodoxime Acid [15, 16]. Now bioavailability of Cefpodoxime Proxetil can be improved simply by increasing solubility or by eliminating pre absorption conversion of Cefpodoxime Proxetil to Cefpodoxime Acid [13, 17].

Hence formulation needs to be prepared for Cefpodoxime Proxetil, which can bypass the passage of drug through epithelial cells and provide sufficient protection to drug through luminal cholinesterase. Hence in order to improve bioavailability, formulation enabling lymphatic absorption such as lipid solutions, micellar solutions, self-emulsifying drug delivery system, solid lipid nano particles, and recently, micro emulsions and nano emulsions can be prepared of Cefpodoxime Proxetil [18, 19].

In present work, Micro emulsion of Cefpodoxime Proxetil is prepared using pseudo ternary phase diagram. The concentration of Surfactant: Co surfactant is varied. All the prepared batches were evaluated for pH, viscosity, globule size, zeta potential, centrifugation, freeze thaw, and dilution. Batches were further evaluated for *in-vitro* drug release and drug content. To confirm the efficacy of the product antibiotic assay was also performed.

**MATERIALS AND METHOD:****Drugs and Reagents**

Cefpodoxime Proxetil was gifted by Nectar Pharmaceuticals. Capmul MCM was gifted by Across Chemicals, Mumbai. Tween 80 and PEG 400 were purchased from S.D Fine Chemicals, Mumbai.

**Calibration Curve of Cefpodoxime Proxetil**

Cefpodoxime Proxetil of 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70 and 75 µg/ml were prepared in 0.1 N HCl and  $\lambda_{max}$  values were determined by scanning these solutions against the reagent blank [0.1 N HCl] in the range of 200–400 nm [UV-Vis spectrophotometer, Shimadzu 1700, Kyoto, Japan] [20].

### Pseudo ternary Phase Diagrams

The pseudo ternary phase diagrams containing oily phase, surfactant, co surfactant, and water were developed by the spontaneous emulsification method. The ratio of surfactant and co surfactant [ $S_{mix}$ ] [0.5:1, 0.75:1, 1:1] in fixed weight ratios were then mixed with oil at ambient temperature. For each phase diagram, the ratio of oil to the  $S_{mix}$  was varied as 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9 [v/v]. Water was added drop wise to each oil- $S_{mix}$  mixture under vigorous stirring. After equilibrium, the samples were visually checked and determined as being clear micro emulsions. No heating is conducted during the preparation. Phase diagrams were prepared using CHEMIX School Ver. 3.50 software [MN, USA]. The mixture compositions at different points in the phase diagrams were defined by the expression [21].

$\%A [Capmul\ MCM] + \%B [Tween\ 80 + propylene\ glycol + transcitol] + \%C [water] = 100.$

### Preparation of Micro Emulsion

The Micro Emulsions of Cefpodoxime Proxetil were prepared by the spontaneous emulsification method [titration method]. The calculated amount of drug [100mg] was added to the oily phase Capmul MCM [2%] and magnetically stirred [REMI Enterprises] until dissolved followed by the addition of Surfactant Tween 80 [20%] and Co Surfactant PEG 400 [5.71%] mixture in a fixed proportion [0.5:1, 0.75:1, 1:1] to produce a clear mixture. Finally this mixture was titrated with distilled water to produce micro emulsion of Cefpodoxime Proxetil [22].

### Evaluation parameters

#### pH determination

The apparent pH of all the selected micro emulsions was determined at 25°C by immersing the electrode directly into the micro emulsions using a digital pH meter [Corning, Model 10 England] [23, 24].

#### Viscosity measurement

Micro emulsions are generally low viscosity systems. The viscosity of the prepared micro emulsion was measured at 25°C at 60 rpm by LV spindle no. 63 using a Brookfield viscometer [model LVDVE230; Brookfield Engineering Laboratories, Inc] [25].

#### Globule size

The globule sizes of prepared micro emulsions were analyzed using Micro-Tract Nano-Tract ZS. A graph was plotted for size in nm against % of intensity. The size where there was maximum intensity was observed in the mean globule size of the formulations. Particle size analysis was performed to confirm that the size range of micro emulsion [26].

### Zeta potential

A laser Doppler electrophoresis was carried out on the microemulsions with a Zeta seizer Nano Series equipment [Malvern Instruments, UK] [27].

### Freeze thaw cycle

The prepared batches were subjected to alternate freeze thaw cycles. Each ratio was subjected to refrigeration temperature i.e -20°C for 24 hrs and for the next 24 hrs they were subjected to room temperature. Likewise 3 freeze thaw cycles were carried out and the batches was observed for any phase separation, drug precipitation or any instability [28, 29].

### Centrifugation

Batches that passes the freeze thaw cycle test are further subjected to centrifugation. The mixture is centrifuged at 4000 rpm for 15minutes and again observed for any signs of phase separations or drug precipitation [30, 31].

### Robustness to dilution

Robustness of prepared batches to dilution was studied by diluting it 100 times with water. The diluted micro emulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation [32].

### In-vitro drug release studies

The in vitro drug release of Cefpodoxime Proxetil from the micro emulsion formulations was determined by dialysis bag method. 0.1N HCl as medium for in vitro release studies. 5ml of formulation was placed in the dialysis bag [single dose containing 100 mg of Cefpodoxime Proxetil], which was immersed in 50ml of 0.1 N HCl for 2 hrs maintained at 37°C and stirred with a magnetic stirrer. Samples were withdrawn at predetermined time intervals. In order to maintain sink conditions, an equal volume of medium was replaced. The samples were analyzed by the UV-Visible spectrophotometer at 264 nm to determine the concentration [33].

### Drug Content

The drug content evaluation for the selected batches was done by dissolving 100 mg of drug to 5 ml of the particular formulation. These drug loaded formulations were subjected to assay by analyzing it in UV spectrometer at respective  $\lambda_{max}$  [34]. The percentage drug content was then calculated by the formula,

$$\% \text{ Drug content} = \frac{Ma}{Mth} \times 100$$

Where, Ma = actual drug content in the formulation  
Mth= Theoretical drug content in the formulation

### Antimicrobial Assay

All 3 batches containing Cefpodoxime Proxetil were used to conduct antibiotic assays in an aseptic area. The prepared micro emulsions and pure

Cefpodoxime Proxetil in solution form were placed in the cups of nutrient agar plates containing E.Coli were placed in an incubator at 37°C for 18 hrs [35].

### RESULT AND DISCUSSION:

#### Calibration Curve of Cefpodoxime Proxetil

The  $\lambda$  max of Cefpodoxime proxetil was found to be 264 nm. [Figure 1]

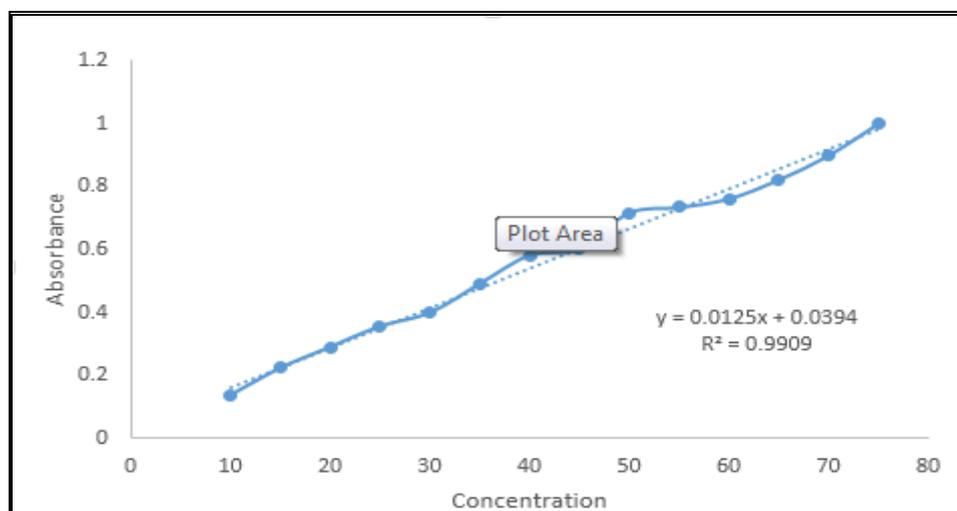


Figure 1: Calibration Curve of Cefpodoxime Proxetil

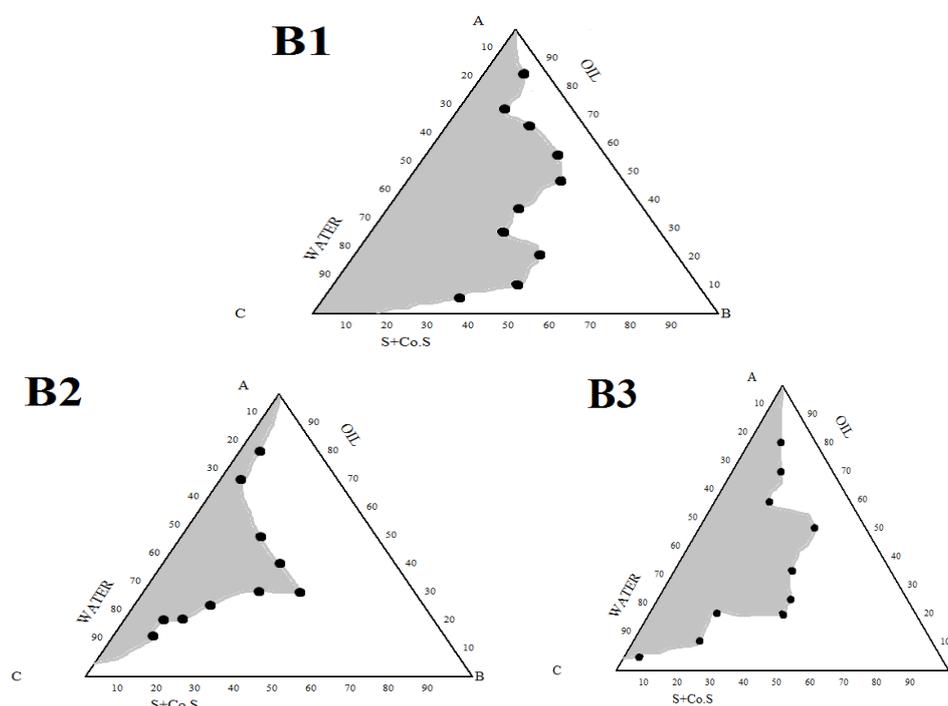


Figure 2: Phase diagrams of B1, B2, B3

#### Pseudo ternary Phase Diagrams

Pseudo-ternary phase diagrams were constructed by using Capmul MCM [oil], Tween 80 [surfactant] and PEG 400 [co-surfactant]. The  $S_{mix}$  weight ratios [[0.5:1, 0.75:1 and 1:1] are represented in Figure 2. In pseudo ternary phase diagram the Micro emulsion area is presented as shaded region.

The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual identification. From these phase diagrams, the influence of relative surfactant: co-surfactant concentrations on the micro emulsion isotropic region can be evidently seen [36].

**pH and Viscosity**

The pH value was found to be in the range of 6.2 to 6.4 for batches B1 to B3. All batches B1 to B3 were found to have viscosity ranging from 48.18 to 70.92 poise. The viscosity of the micro emulsion increased with increasing concentration of the surfactant [22]. The results are shown in table no. 1.

**Table 1: Results of pH and Viscosity**

Batch Code	pH	Viscosity [Poise]
B1	6.2	48.18
B2	6.4	60.74
B3	6.3	70.92

**Globule Size and Zeta Potential**

Globule size analyzer Micro-Tract Nano-Tract ZS was employed to determine the globule size of all the three formulations. The globule sizes were

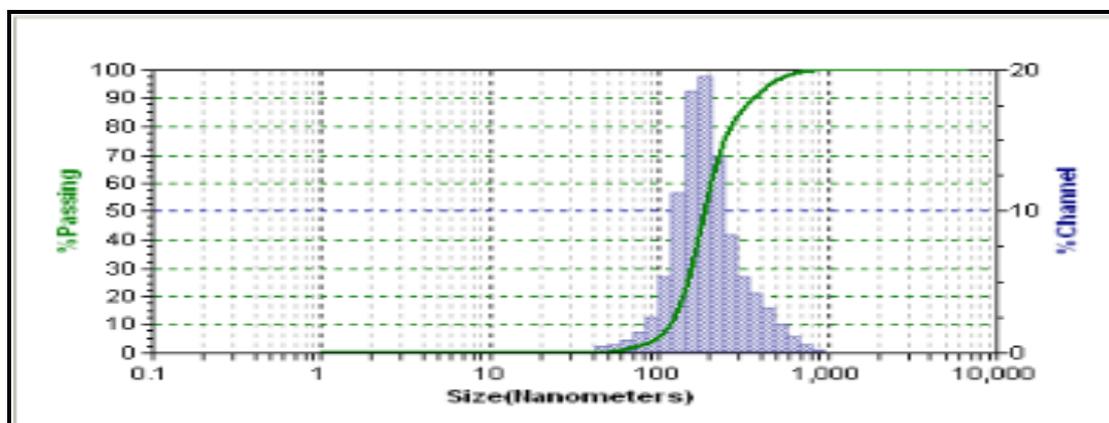
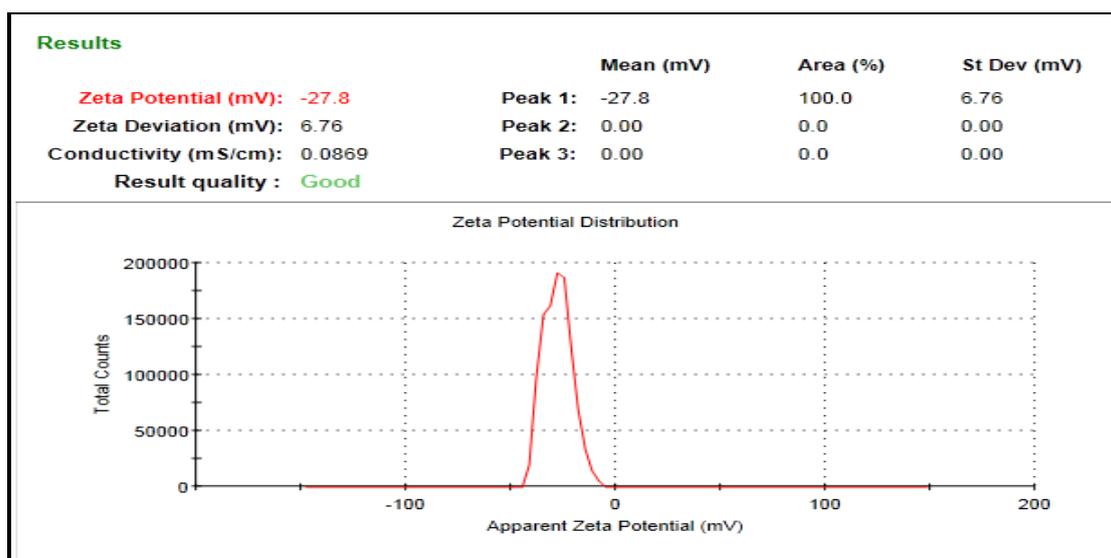
found to be in range of 185 to 888 nm. This shows that the prepared formulations were micro sized and could be rightly termed as micro formulations [37].

The zeta potential of the prepared batches were of the range -26.3 to -27.8. This shows that all the prepared formulations were stable.

The results found are shown in table no. 2, figure no. 3 and figure no. 4.

**Table 2: Results of Globule Size and Zeta Potential**

Batch Code	Globule Size [nm]	Zeta Potential
B1	888	-26.3
B2	510	-26.6
B3	185	-27.8

**Figure 3: Particle Size Report of Batch B3****Figure 4: Zeta Potential Report of Batch B3**

### Centrifugation, Freeze thaw cycle, Robustness to dilution

Micro emulsions are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and Co-surfactant with no phase separation, creaming or cracking. Hence centrifugation was carried out on the prepared formulations. In the current investigations all the batches passes the centrifugation test. No signs of phase separation or drug precipitation were seen.

All the batches were then subjected to freeze thaw cycle. At the end of 3rd cycle Batch B1 and B3 were stable but B2 was found to be unstable.

Robustness to dilution was carried out to check the stability of the micro emulsions. All the three batches were diluted up to 100 times with distilled water to check if phase separation occurs. But all the three batches passed the test [30, 31, 32].

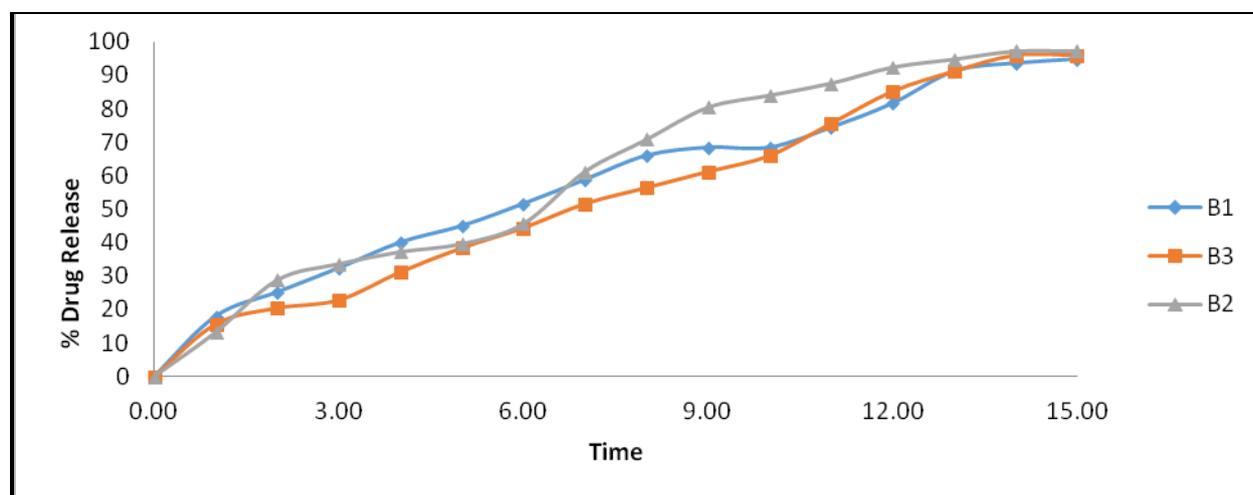
The results found are shown in table no. 3

### % Cumulative drug release studies and Drug content

The cumulative drug content permeated from the membrane for all B1, B2 and B3 was calculated. *In Vitro* release profiles and drug content of Cefpodoxime Proxetil across the cellophane membrane from the micro emulsion system containing capmul MCM [oil], tween 80 [surfactant] and PEG 400 [co-surfactant] of batch B1, B2 and B3 are shown in table no. 4. The cumulative amount of drug permeated through the cellophane membrane from different micro emulsion formulations was calculated. Almost complete drug release [90–100%] was obtained within 15 hrs. Drug release of Batch B1 was lower than that of Batch B2. Drug release was more for the Batch B3. Thus, all the three batches appears to be suitable for obtaining a sustain release effect [Figure. 5] [38, 39].

**Table 3: Results of Centrifugation, Freeze thaw cycle, Robustness to dilution**

Batch Code	Freeze Thaw	Centrifugation	Robustness to dilution
B1	Pass	Pass	Pass
B2	Fail	Pass	Pass
B3	Pass	Pass	Pass



**Figure 5: % Cumulative Drug Release**

**Table 4: Results of % Cumulative Drug Release and Drug Content**

Batch Code	%CDR	Drug Content [mg]
B1	94.8	96.6
B2	96	98.3
B3	97.2	98.1

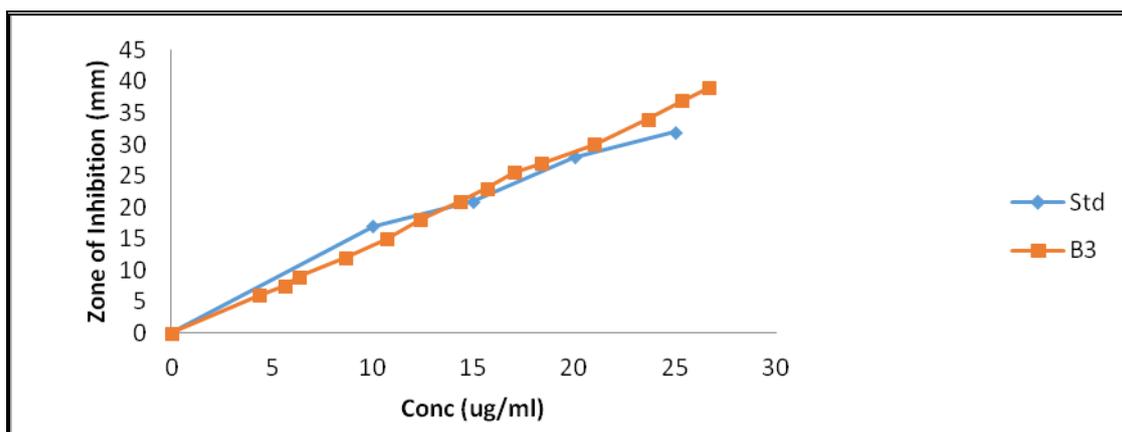


Figure 6: Anti-Microbial Assay of standard and B3

#### Anti-Microbial Assay

Results of Batch B3 and Standard [API] are shown in figure No. 6. Batch B3 shows zone of inhibition of 39mm at 26.6 [ug/ml] and Standard shows zone of inhibition of 32 mm at 25[ug/ml]. This proves that the prepared micro emulsion shows better efficacy towards the organisms [40].

#### CONCLUSION:

The optimized micro emulsion batch B3 containing Capmul MCM as oil [2%], Tween 80 as surfactant [20%], PEG 400 as co-surfactant [5.71] and distilled water [72.29%] was a transparent, clear and low viscosity system, with particle size 185 nm. The zeta potential was found to be -27.8 which shows that the prepared micro emulsion was stable. The micro emulsion showed the viscosity 70.92 poise and pH was found to be 6.3. B3 passes the centrifugation test and three days freeze thaw stability test. B3 was diluted up to 100 times and it also passes the dilution test. The drug content was found to be 98.1%. The prepared micro emulsion showed the % cumulative drug release of about 97.2% up to 15 hours. Antimicrobial assay was also performed and it showed satisfactory results. Thus, it can be concluded that Cefpodoxime Proxetil having poor solubility can be formulated as micro emulsion, which increase the solubility of the drug and hence, which will increase its oral bioavailability than the other dosage forms.

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