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FABRICATION AND *IN-VITRO* EVALUATION OF CEFIXIME NANOPARTICLES USING GUM KONDAGOGU AND CHITOSAN AS MATRIX FORMERS

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Keywords:

Cefixime, Gum Kondagogu, Chitosan, Sustained drug release

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ABSTRACT: Cefixime is more effective in treating multi drug resistant typhoid fever but the major limitation was its poor bioavailability with short half- life. The present investigation was attempted to develop a natural polymer based nanoparticles containing cefixime using gum kondagogu and chitosan as polymers for customising the drug release profile to achieve an effective therapeutic concentration by increasing its solubility and bioavailability. The cefixime nanoparticles were prepared by the modified coacervation method and evaluated for particle size, zeta potential, morphological studies (SEM, TEM and AFM), entrapment efficiency, *in-vitro* drug release studies and *in-vitro* antimicrobial efficiency studies. The prepared drug nanoparticles found to be average mean particle size in range from 80.6±3.5 to 230.6±7.3nm and entrapment efficiency was found to be 78.0±1.5 to 93.2±2.5%. The *in-vitro* drug release showed a biphasic pattern with initial burst release followed by sustained drug release up to 32h. The MIC50 of prepared formulation was one fold lesser than pure cefixime for *Salmonella* Typhi isolates. The disc agar diffusion (DAD) test confers that the zone of inhibition was found to be better for the formulation against pure cefixime. In conclusion, the developed Cefixime nanoparticles support to customise the drug release profile and better zone of inhibition with minimum concentration which provoke better patient compliance.

INTRODUCTION: Typhoid fever is a life-threatening illness caused by the bacterium *Salmonella* Typhi, usually through the consumption of contaminated food or water. According to World Health Organisation, approximately 21 million cases and 2, 22,000 typhoid deaths were found to be reported annually throughout the world. Flouroquinolones are the drug of choice for the management of typhoid fever but unfortunately, they are contraindicated in paediatric patients and pregnant women due to its damage to the articular cartilage.

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Cefixime, oral third generation cephalosporin antibiotic was reported to be more effective in treating Multi Drug Resistant (MDR) typhoid fever particularly in children from endemic areas but the major limitation with cefixime was its poor solubility in biological fluids and thus leading to poor bioavailability (40-50%) and with a half-life of 2-3 h. Therefore, it leads to the administration of 200mg twice daily for 7-14 days. Improper dosage regime may leads to the development of antibiotic resistance. To overcome, the limitations associated with current dosage regimen a novel drug delivery approach is necessary [1].

Nanotechnology has emerged as a promising approach for the treatment of enteric infectious diseases by targeting and sustaining the drug release inside the targeted cells [2]. Additionally nanotechnology offers the advantage of enhancing drug solubility and bioavailability of the poor

soluble drugs and thus leading to reduced dosage of drug, side effects and cost with enhanced therapeutic efficacy and will provoke better patient compliance [3].

In recent years, bio-degradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices due to their applications in drug targeting to particular organs/tissues as carriers [4]. Gums and mucilage are extensively used natural materials for conventional and novel dosage forms. These natural polymers have benefits over synthetic polymers, as they are stable chemically, biocompatible, less toxic, economical, biodegradable, and easily available [5-7].

Gum kondagogu (GK) is an exudate tree gum from the tree (*Cochlospermum gossypium* DC.) belonging to family Bixacea. The most important sugars were found to be neutral sugars (arabinose, mannose, rhamnose, galactose, α-D-glucose, β-D-glucose) and uronic acids (D-glucoronic acid and β-D-galacturonic acid). It can be used as suspending agents and matrix formers for controlled drug delivery due to its gelling property [8]. Chitosan is the cationic deacetylated form of chitin obtained from exoskeletons of marine arthropods [9, 10].

Chitosan gained interest in nanoparticulate oral delivery vehicle because it is able to reduce the trans epithelial resistance and opening the tight conjunction between epithelial cells and due to its good mucoadhesive property it has been used as a carrier for sustained drug delivery but the major limitation of chitosan is restricted by its faster dissolution in stomach and its limited capacity for controlled drug release [11, 12]. To overcome the limitations associated with chitosan poly electrolyte complexes are formed by interactions between molecules that carry oppositely changed ionisable groups and also avoid the use of crosslinking agents, stabilizers and organic solvents [13].

The study was aimed to develop and to evaluate a natural polymer based cefixime nanoparticles prepared using chitosan and gum kondagogu as matrix formers to customise the drug release profile and better zone of inhibition with minimum concentration for improving the patient compliance followed by the declining the limitations associated with conventional dosage forms.

MATERIALS AND METHODS:

Cefixime was obtained as a gift sample from Kniss laboratories Pvt. Ltd, Chennai, India. Gum kondagogu (grade-1) was procured from Girijan Co-operative Corp Ltd, Hyderabad, India. Chitosan was procured from Sigma-Aldrich Chemical Co. Ltd. All other chemicals used were of analytical grade and double distilled water was used throughout the experiments.

Preparation of Gum kondagogu solution:

Gum kondagogu powdered in a high-speed mechanical blender and the polymer solution was prepared according to the procedure described previously and the obtained polymer solution was freeze dried and stored in desiccator until further use [14].

Preparation of deacetylated gum:

Deacetylated gum kondagogu was prepared as per earlier reported method [15]. The deacetylation was monitored by FT-IR spectroscopy.

Structural characterization of deacetylated gum kondagogu by FT-IR, GC-MS, XRD:

The FT-IR spectrum of deacetylated gum was recorded on FT-IR spectrophotometer. The sample were mixed with KBr in ratio of (1:4) and pressed into pellets under mechanical pressure using hydraulic press. The scans were obtained with a spectral resolution of $2cm^{-1}$ from wave number 4000 to 200 cm^{-1} [16]. The GC-MS analysis was carried out using HP-5 conventional capillary column (30m x 0.25mm with internal diameter of 0.25µm) coupled to ion trap mass spectrometry functioned at 70ev. The columns were automated from 50 to 250 ^0C at 50^0C/min [17]. For characterization of crystallinity, X-ray diffraction patterns of gum were carried out using Schimadzu, XRD 6000 equipment, with nickel filtered tube CuKα1 at a voltage of 45 kV and current of 45 mA, The scanned angle was set at 2Θ from 5º to 90º and scanned rate was 1º/min [18].

Drug-polymer compatibility studies:

FT-IR, XRD and proton NMR studies were carried out to determine the possible interaction between

the drug and excipients used. FT-IR and XRD analysis were carried out as reported earlier. The proton NMR spectrum of deacetylated gum was recorded in an NMR spectroscopy (varian, UNITY-400, Switzerland). 100 mg of sample was dissolved in D_2O and chemical shifts were reported in ppm relative to an internal standard TMS (tetramethylsilane) for ^1H NMR. The proton NMR spectrum was obtained at a base frequency of 400MHz and with 16 transitions at a delay time 2 seconds. The chemical shifts were expressed in δ (ppm) relative to the resonance of internal TMS. The existence of an interaction is detected by the alteration, shift or disappearance of a characteristic peak of the drug

Preparation of cefixime nanoparticles:

The purified gum solution of 0.04% w/v was dissolved in distilled water and kept under magnetic stirring and pH of the solution was adjusted to 5.2 using 0.1N hydrochloric acid. The chitosan of 0.02% w/v was dissolved in a solution of 0.1% v/v acetic acid was kept under magnetic stirring and pH of the solution was adjusted to 5.5 using 1N sodium hydroxide, a constant amount of cefixime 0.05% (w/v) was added to the chitosan solution with constant stirring at 3500 rpm. The gum solution was added slowly drop wise to the mixture of chitosan and cefixime at a different polymeric ratios to give four different formulations i.e., F1 (1:1), F2 (2:1), F3 (1:2), F4 (2:2) by modified coacervation method at 12000 rpm for 45 min and then freeze dried and the nanoparticles were stored in desiccator [19, 20].

Physicochemical characterization of cefixime nanoparticles:

Particle size, poly dispersity index and zeta potential:

Nanoparticles size distribution and zeta potential was determined using Nanoparticle analyser SZ-100. The size distribution analysis was performed at a scattering angle of 90° and at a temperature of 25°C using samples appropriately diluted with Isopropanol. The poly dispersity index (PDI) is a dimensionless measure for the broadness of a particle size distribution and can be used for the nanoparticle dispersion. PDI between 0.03 and 0.06 can be denoted as monodisperse, between 0.1and 0.2 as narrowly distributed and between 0.25-0.5 as broadly distributed and value above 0.5 indicated extremely broad size distribution that cannot be described by means of PDI. The zeta potential was measured using a disposable zeta cuvette using samples appropriately diluted with double distilled water.

Morphological analysis:

The morphology of nanoparticles was studied using a scanning electron microscope (Hitachi S 3000H, Japan). The sample was fixed to the plate surface with double-sided adhesive tape and sputtered coated with gold as the samples were non-conducting and surface morphological features were observed.

Transmission electron microscopy (TEM) was used to study the surface morphology of nanoparticles. A small aliquot of nanoparticles suspension were dropped onto formvar-coated copper grids and dried in hot air oven for 45 min then the samples were stained using 2% w/v phosphotungstic acid at room temperature. The picture was captured using Digital Micrograph and soft imaging viewer software (Olympus, Germany) was used for capturing and analysis [21].

The morphological characteristics of cefixime nanoparticles were observed using Atomic Force Microscopy (AFM). The small quantity of sample was dissolved suitably in Isopropyl alcohol was deposited on a glass slide and dried overnight to form a thin film and was analysed by AFM (NT-MDT).

Determination of % Encapsulation efficiency and % drug content:

The percentage encapsulation efficiency of drug loaded nanoparticles was determined by separating unentrapped drug from the nanoparticles by centrifugation at 12,000 rpm at 5^0 c for 45 min. The amount of cefixime in supernatant was determined spectrophotometrically by measuring the absorbance in UV-Vis spectrophotometer at 287 nm [22-24].

$$\% \text{ Encapsulation efficiency} = \frac{\text{(Actual drug content)}}{\text{(Theoretical drug content)}} \times 100$$

$$\% \text{ Drug content} = \frac{\text{(Weight of drug in nanoparticles)}}{\text{(Weight of nanoparticles)}} \times 100$$

$$\%\text{Yield} = \frac{\text{(Weight of nanoparticles recovered)}}{\text{(Weight of the polymer and drug fed initially)}} \times 100$$

***In-vitro* drug release by diffusion bag technique:**

In-vitro drug release studies for the nanoparticles were performed using diffusion bag technique. The cefixime nanoparticles (equivalent to 10mg) dispersed in 5ml of dissolution medium was placed in a dialysis bag (MWCO: 12–14 kDa, surface area of 22.5 cm^2) immersed in USP Apparatus I with a dissolution medium (300ml) of 0.1 M potassium phosphate buffer of pH 7.4 stirred at 37 ±2°C maintained at 100 rpm [25]. 1ml of sample was withdrawn at regular intervals of time and an equal volume of buffer solution was added to maintain the constant volume of dissolution medium. The amount of drug released was measured spectrophotometrically using UV at 287nm. All measurements were performed in triplicate (n=3) and SD was calculated [26].

Drug Release Kinetics:

The results obtained from *in-vitro drug* release studies were attempted to fit into various mathematical models such as Zero order release kinetics, First order release kinetics, Higuchi classical diffusion equation, Koresmeyer-Peppa's exponential equation and Hixson-Crowell erosion equation to know the mechanism of drug release. The equation with high regression coefficient (r^2) for formulation will be the best fit of release data. For Koresmeyer-Peppa's equation, if n = 0.5 indicating pure fickian diffusion, n = 0.5-1 indicating anamolous non-fickian diffusion and n=1 indicates zero order release [27, 28].

***In-vitro* antimicrobial efficiency:**

Stock cultures of *Salmonella Typhi* were kept at 4°c on slant. The active cultures required for the experiment were prepared by transferring a loop full of culture from the stock cultures to test tubes containing nutrient broth and incubated for 24 h at 37ºc.

Disc agar diffusion technique:

The antibiotic-resistant profile of sample was determined by disc diffusion method to determine the zone of inhibition. The study was carried out on Muller Hinton agar (MHA) medium prepared by weighing 3.8 g and dissolved in 100ml of distilled water to this 1gm of agar was added and kept for sterilization. After sterilization the MHA media was poured in to sterile petriplates and were allowed to solidify for thirty minutes. Then the inoculums were spread on to the solid plates with sterile swab moistened with the bacterial suspension. Add 20 µl of sample serially diluted to a concentration of 62.5 µg, 125 µg, 250 µg, 500 µg and 1000 µg/disc placed on MHA plates. These plates were incubated for 24 h at 37ºc .Then the activity was determined by measuring the diameter of zone of inhibition [29].

Broth Dilution technique:

5 ml sterilized nutrient broth was taken in each tube. To this 100 µl of culture was added and then 100 µl of different concentration of samples was added. OD was measured at 620 nm [30].

RESULTS AND DISCUSSION:

Structural characterization of deacetylated gum kondagogu by FT-IR, GC-MS, XRD:

The FT-IR spectra indicates the presence of broad band in the FT-IR of gum at 3419.26 cm^{-1} indicates the N-H (amide) stretching mode and O-H (hydroxyl) groups, the characteristic peak at 1080.47 and 2923.85 cm^{-1} corresponds to C-O as well as C-H stretching band, the characteristic absorption peak at 1605.46 cm^{-1} corresponds to C-O stretching and N-H bending vibrations, the peak at 1030 cm^{-1} represents stretching mode of carboxylic acid of D-glucoronic acid, the bands at 707.76 and 538.12 cm^{-1} indicated the N-H wagging vibrations. The absence of peaks at 1736 cm^{-1} and 1227 cm^{-1} were attributed to acetyl groups which were absent in deacetylated gum (**Fig. 1**).

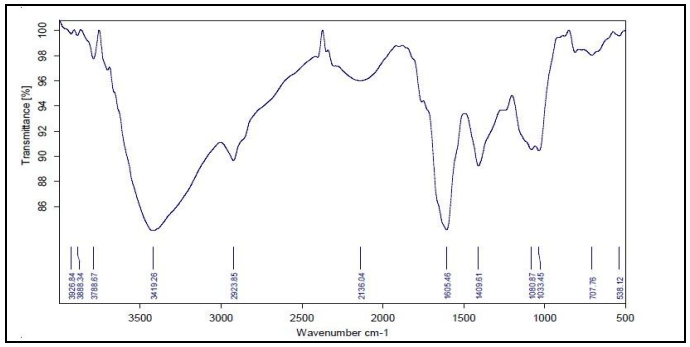

FIG. 1: FT-IR SPECTRA OF GUM KONDAGOGU

The GC-MS of hydrolysed fraction showed four peaks at retention time (RT) 16.08min, 8.75 min, 14.27 min, 12.18 min, 9.87 min, 7.42 min and 5.2 min , with molecular ion peaks of mass/charge (m/z) ratio 218.41, 206.69, 220.75, 194.00, 178.64, 132.72 respectively confirmed the presence of D-galactose and D-galacturonic acid (**Fig. 2**).

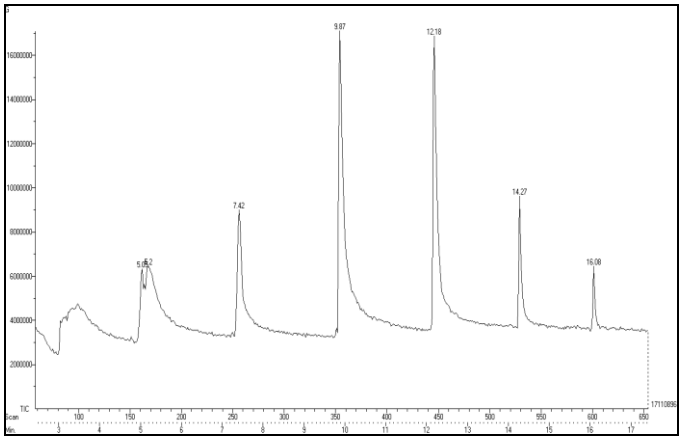

FIG. 2: GC-MS ANALYSIS OF ACID BASE HYDROLYSED FRACTION OF GUM

From XRD pattern no characteristic peaks were observed indicates that the gum was found to be in amorphous form **(Fig. 3**).

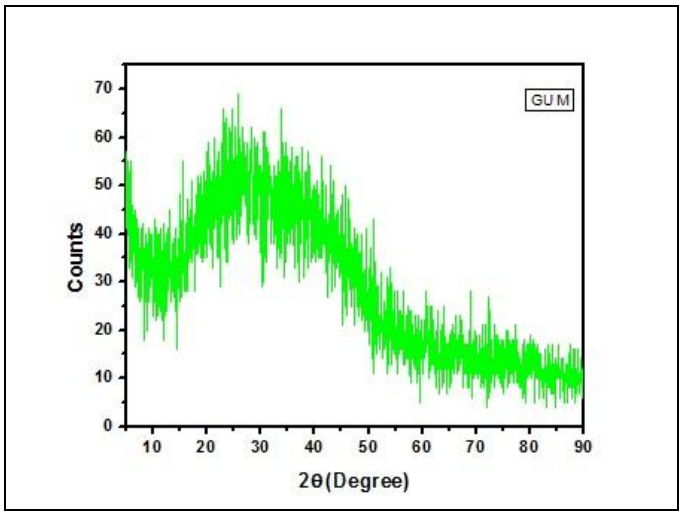

FIG. 3: X RAY DIFFRACTION PATTERN OF GUM

Drug-polymer compatibility studies:

The FT-IR spectra of cefixime, gum kondagogu, chitosan and its physical mixture containing drug and polymer were analysed (**Fig. 4).** There were no changes in the peak shape and peak position of drug in the physical mixture containing drug and polymer used. Hence spectra indicate that there were no incompatibility between drug and excipients.

The X-ray diffraction pattern of drug and the formulation were carried out. The pure drug confers crystalline nature with sharp peak between 7.96^{o} [^{o}2Th.] to 26.37 [^{o}2Th.] a characteristic of cefixime that represent the crystalline nature of the drug, the same diffraction was also observed in the prepared formulation with decreased intensity of signal indicating no signs of incompatibility between the pure drug and formulation components (**Fig. 5**).

The proton NMR spectra of cefixime and its physical mixture indicate no significant differences in the characteristic proton assignments of the drug compared to its physical mixture with the polymers. Hence the polymer was compatible with the drug (**Fig. 6**).

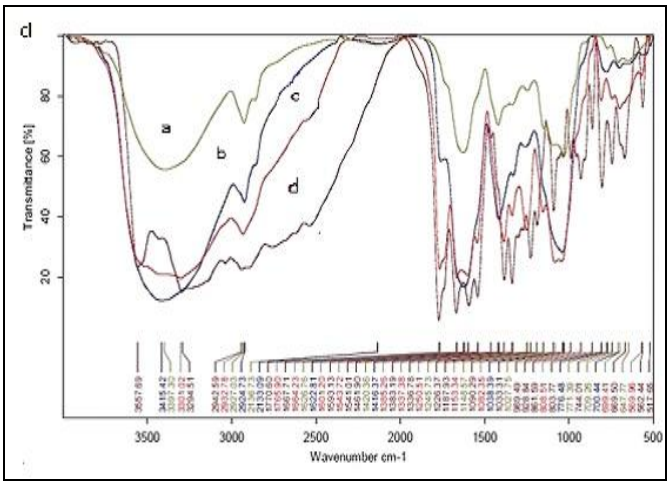

FIG. 4: FT-IR SPECTRA OF PHYSICAL MIXTURE CONTAINING DRUG AND POLYMERS: A) GUM KONDAGOGU B) CHITOSAN C) PHYSICAL MIXTURE D) CEFIXIME

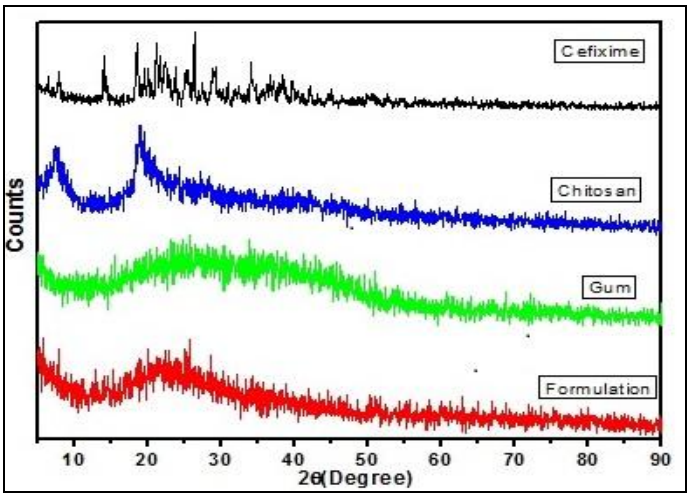

FIG. 5: XRD PATTERN OF CEFIXIME, CHITOSAN, GUM KONDAGOGU AND PHYSICAL MIXTURE CONTAINING DRUG AND POLYMERS

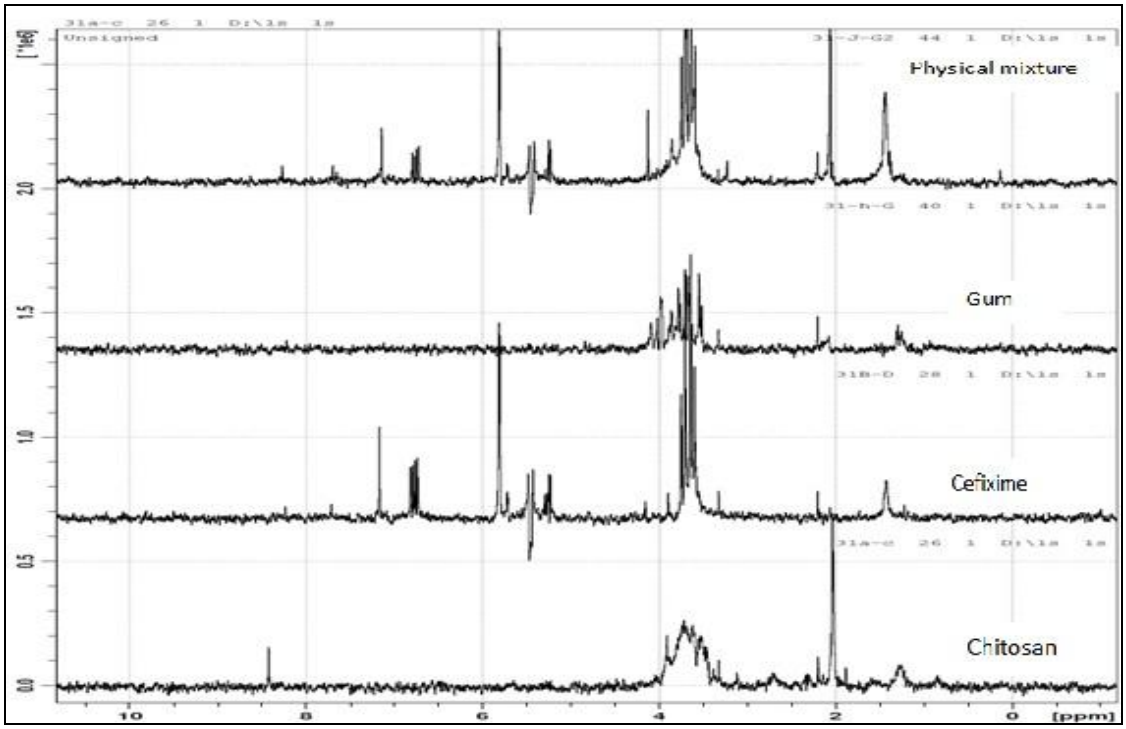

FIG. 6: NMR SPECTRA OF CEFIXIME, CHITOSAN, GUM KONDAGOGU AND PHYSICAL MIXTURE CONTAINING DRUG AND POLYMERS

Physicochemical characterization of cefixime nanoparticles:

Particle size and zeta potential: The average particle size was found to be increased with increase in polymer concentration. The poly dispersity index was found to be proportional with the particle size. Surface charge on the particles could control the particles stability of the nanoparticulate formulation through strong electrostatic repulsion of particles with each other. The Formulations F2 and F3 with Zeta Potential < -30 mV and > +30mV respectively, shows high degrees of stability with no aggregation. In addition, from the zeta potential measurement, the dominated component on the particles surface for formulation F2 was predicted as gum, being negatively charged polymer imparts anionic nature to nanoparticles, whereas for F3 the dominated component on the particles surface was predicted as chitosan which imparts cationic nature to the nanoparticle. The zeta potential value for F1 and F4 formulations was found to be approximately neutral **(Table 1**).

TABLE 1: CHARACTERIZATION OF FORMULATIONS FOR AVERAGE PARTICLE SIZE, POLY DISPERSITY INDEX AND ZETAPOTENTIAL*

Formulation	Average Size mean (nm)	Polydispersity index	Zetapotential (mV)
F1	80.6±3.5	0.171±0.03	11.7±0.95
F2	91.6±4.6	0.219±0.05	-52.1±0.56
F3	155.2±7.0	0.436±0.02	31.4±1.24
F4	230.6±7.3	0.576±0.03	14.4±0.98

*Data represented as mean ± SD (n=3)

Morphological analysis:

The SEM studies, surface morphology of the prepared formulation was found to be spherical, rod shaped with smooth surface (**Fig. 7**). The TEM images indicates that the nanoparticles with spherical shape in size range between 76 nm to 223 nm and appeared to be in same diameter as compared to average particle size measured using nanoparticle analyser (**Fig. 8**). The AFM studies confirmed the presence of spherical and dense solid nanoparticles (**Fig. 9**) and three-dimensional view of the nanoparticles showed that the nanoparticles are discrete with average particle size of 83 nm.

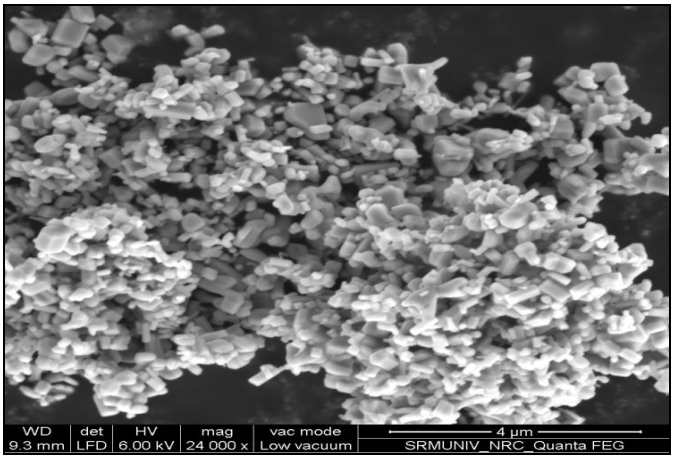

FIG. 7: SEM MICROGRAPH OF CEFIXIME NANOPARTICLES

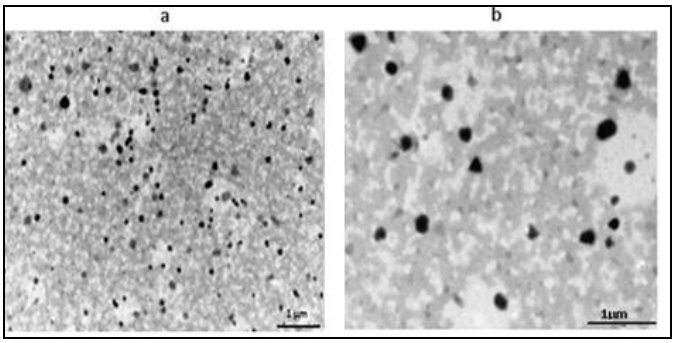

FIG. 8: TEM MICROGRAPH OF CEFIXIME NANOPARTICLES

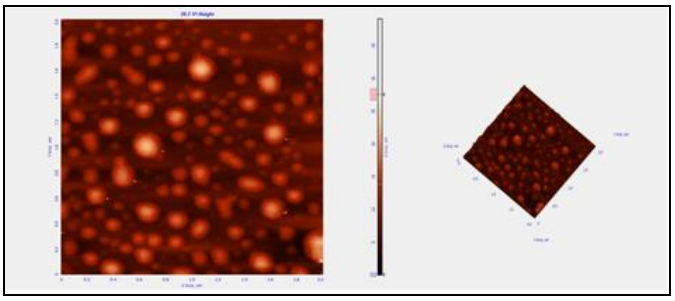

FIG. 9: AFM MICROGRAPH OF CEFIXIME NANOPARTICLES

Determination of % entrapment efficiency, % drug content and % yield:

The % entrapment efficiency of the cefixime nanoparticles was found to in the range from 78.0±1.5 to 93.2±2.5. The % drug content was found to be in the range from 62.5±1.6 to 95.1±2.2 and % yield was found to be in the range from 40.43±1.3 to 47.15±0.9. The % entrapment efficiency and % drug content was found to be increased with increase in polymer concentration, but in formulation F4 due to increase in size the surface area of nanoparticles was decreased which in turn decreased the drug entrapment efficiency and drug content. The % yield was found to be increased with increase in polymer concentration (**Table 2).**

TABLE 2: CHARACTERIZATION OF FORMULATIONS FOR % ENTRAPMENT EFFICIENCY AND % DRUG CONTENT*

Formulation	% Entrapment efficiency	%Drug content	% Yield
F1	83.6±1.1	92.9±1.5	40.43±1.3
F2	93.2±2.5	95.1±2.2	45.45±0.2
F3	88.6±1.6	93.7±0.5	44.52±1.6
F4	78.0±1.5	62.5±1.6	47.15±0.9

*Data represented as mean ± SD (n=3)

***In-vitro* drug release by diffusion bag technique:**

From *in-vitro* drug release study by bag diffusion technique showed a biphasic pattern with initial burst release followed by sustained release of drug up to 32h. The F2 showed sustained drug release compared to other formulations. The amount of drug release was decreased with increase in polymer concentration due to increase in the thickness of the polymeric membrane which decreases the diffusion of drug through it (**Fig. 10**).

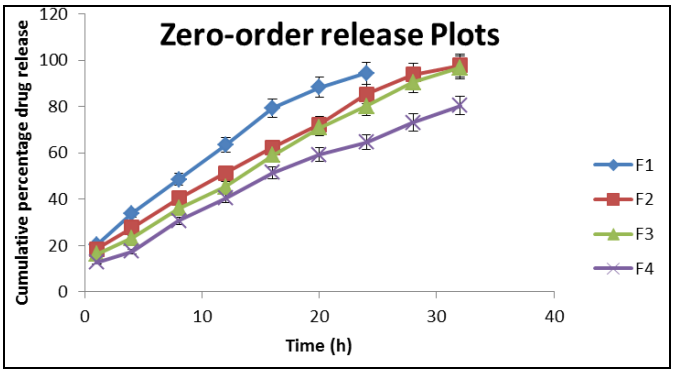

FIG. 10: *IN-VITRO* DRUG RELEASE PROFILE OF PREPARED FORMULATIONS

Drug release kinetics:

The results obtained from the data was extrapolated by using different kinetic models revealed that the zero order plots were linear for all the formulations and first order plots were not linear for all the formulations **(Table 3)**. Based on the highest regression coefficient value (r^2) the best fit model for all formulations was found to be Higuchi model (r^2: 0.97-0.98). The release of drug from the polymer matrix containing hydrophilic polymers involves diffusion. To confirm the diffusion mechanism the data was fitted into Koresmeyer-Peppa's equation, as 'n' values indicates between 0.5-1, the mechanism of drug release was found to follow anomalous non-fickian diffusion i.e. the

increased diffusivity of drug from the matrix by solvent-induced relaxation of the polymers.

TABLE 3: CURVE FITTING DATA OF ALL FORMULATIONS

Formulations	Zero order Equation	First order Equation	Higuchi Equation	Koresmeyer Peppa's Equation		Hixson-Crowell Equation
	r^2	r^2	r^2	n	r^2	r^2
F1	0.981	0.960	0.987	0.502	0.986	0.958
F2	0.991	0.892	0.978	0.510	0.964	0.959
F3	0.995	0.881	0.969	0.540	0.953	0.891
F4	0.988	0.982	0.979	0.558	0.955	0.871

In-vitro antimicrobial efficiency:

The antibiotic-resistant profile, as determined by the Disc Agar Diffusion technique reveals that the diameter of zone of inhibition of pure drug and prepared formulation (F2) was found to be 9mm and 14 mm at 125µg/disc which confers that the prepared formulation was found to be exhibiting better zone of inhibition against the pure drug solution. Thus by customising the drug release profile of the cefixime nanoparticles, effective therapeutic concentration was achieved which may overcome the limitations associated with conventional drug delivery systems (**Fig. 11**).

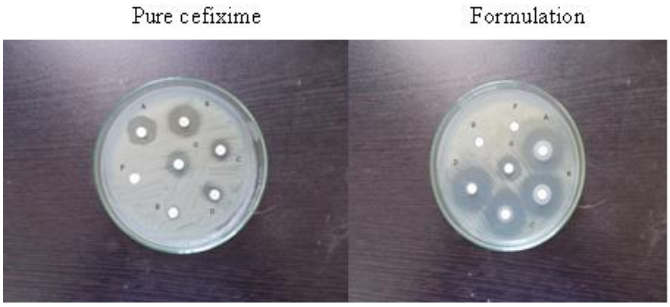

FIG. 11: DETERMINATION OF ZONE OF INHIBITION (mm) BY DISC AGAR DIFFUSION TECHNIQUE OF THE SELECTED FORMULATION (F2) AT DIFFERENT CONCENTRATIONS. A.1000 µg/DISC B. 500 µg/DISC C.250 µg/DISC D.125 µg/DISC E.BLANK F.DMSO (NEGATIVE CONTROL) G. STREPTOMYCIN IN 10µg/DISC

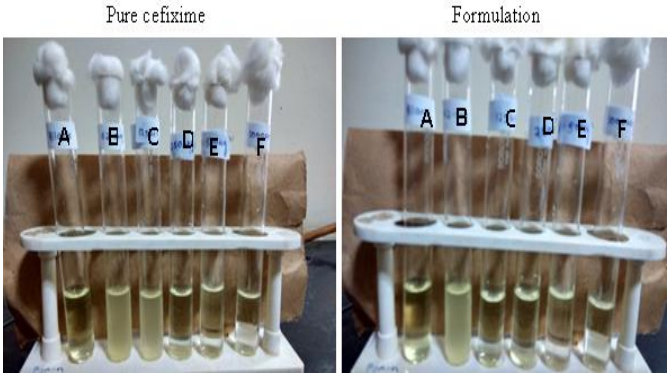

FIG. 12: DETERMINATION OF MIC BY BROTH DILUTION TECHNIQUE OF THE SELECTED BATCH (F2) AT DIFFERENT CONCENTRATION. A. DMSO (NEGATIVE CONTROL) B. 62.5 µg/ml C.125 µg/ml D. 250 µg/ml E. 500 µg/ml F.1000 µg/ml

From the broth dilution technique the MIC50 values of pure cefixime and prepared formulation (F2) for cefixime sensitive *Salmonella* Typhi isolates were determined. The MIC50 value of cefixime nanoparticles and pure cefixime was found to be 125 µg/ml and 250 µg/ml respectively. The MIC50 of prepared cefixime nanoparticles was one fold lesser compared to pure cefixime solution which reveals the better antimicrobial activity of the prepared formulation against pure drug this may be due to the increased bacterial adhesion of cefixime nanoparticles at the site of target (**Fig. 12**).

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