



Formulation, Characterization and Comparison of Cefixime, Cefaclor and Cefdinir Microspheres

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Abstract

The purpose of this research work is to increase and compare the residence time of drugs Cefixime, Cefaclor and Cefdinir by formulating as floating microspheres and to study the effect of formulation variables on microsphere characteristics. Microspheres are prepared by solvent evaporation method. For each drug nine different formulations are prepared by changing drug to polymer ratio, volume of internal phase, volume of external phase and stirring time. The prepared microspheres are characterized for drug - polymer compatibility by IR, percentage yield, particle size analysis, drug entrapment efficiency, and surface morphology by SEM, bulk density, percentage buoyancy, in-vitro release and release kinetic studies. Results of these evaluations showed that particle size in the range of $102.5 \pm 1.3 \mu\text{m}$ to $110.0 \pm 2.21 \mu\text{m}$, $100.8 \pm 1.6 \mu\text{m}$ to $106.2 \pm 1.3 \mu\text{m}$ and $102.1 \pm 1.3 \mu\text{m}$ to $108.6 \pm 1.7 \mu\text{m}$, entrapment efficiency is found to be 75.69 ± 1.91 to $88.35 \pm 2.67\%$, 75.72 ± 1.94 to $92.02 \pm 1.07\%$ and 75.69 ± 1.91 to $89.45 \pm 1.63\%$, drug content is found to be in the range 97.46 ± 2.4 to 98.95 ± 1.8 , 95.55 ± 1.4 to 99.92 ± 2.67 and 96.89 ± 2.1 to 99.11 ± 2.1 respectively. Fourier-Transform Infra-Red (FT-IR) studies ensured that no drug - polymer interaction in the formulated microspheres and the surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. In- vitro release profile of microspheres for F6, F14 and F23 formulations are found to be 97.87 ± 0.22 , 98.45 ± 0.47 and 99.87 ± 0.36 at the end of 12hrs. In release kinetic studies, the F6, F14 formulations followed zero order and F23 formulation followed first order drug release with non-Fickian diffusion mechanism.

Keywords

Cefixime, Cefaclor, Cefdinir, FT-IR, SEM, Microspheres.

INTRODUCTION

Microspheres are defined as solid spherical particles containing dispersed drug in either solution or microcrystalline form. They are ranging in size from 1 to 1000 micrometer. Microspheres are in strict sense, spherical solid particles. Microcapsules are small particles that contains an active agent as a core material and coating agent as shell, at present there is no universally accepted size range that particle must have in order to be classified as microcapsules. However, many workers classified capsules smaller than 1 micrometer as nano capsules and capsules layer more than 1000 micrometer as macro particles. Commercial microcapsules typically have a diameter between 3-80 micrometer and contain 10-90 weight

% cores. Cefixime and Cefdinir are third generation and Cefaclor a second-generation cephalosporin antibiotic drug. The bio availabilities of the drugs are well absorbed with a half-life of 3-5hour and 0.6-0.9 hour for Cefixime and Cefaclor and for Cefdinir 1.7 to 0.6 hour respectively. To increase the bioavailability of the Cefixime, Cefaclor and Cefdinir with reducing dosage frequency microspheres are selected as suitable approach.

MATERIAL AND METHODS

Materials: Cefixime, Cefaclor and Cefdinir are obtained as a gift samples from Hetero drugs, Hyderabad (India). SCMC, HPMCK4M, EUDRAGIT are obtained from Colorcon India pvt.ltd,. Ethanol, DCM, Tween80, Liquid paraffin are purchased from Colorcon India pvt.ltd. All other chemicals and reagents used are of analytical grade.

Preparation of Cefixime, Cefaclor and Cefdinir Microspheres individually by non-aqueous solvent evaporation technique: Microspheres containing Cephalosporin drugs as a core material are prepared by a non- aqueous solvent evaporation method. Drug and different polymer ratio are mixed in the mixture of dichloromethane and ethanol at a 1:1 ratio. The slurry is slowly introduced into 30 ml of liquid paraffin containing 0.01% Tween 80, while stirring at 1200 rpm using a mechanical stirrer equipped with three bladed propellers at room temperature. The solution is stirred for 2 h and the solvent evaporates completely and filtered by using filter paper. The microspheres obtained are washed repeatedly with petroleum ether (40-60 °C) until free it is from oil. The collected microspheres are dried at room temperature and subsequently stored in desiccators.

Physical characterization of microspheres:

Solubility study: Excess drug is added carefully using a spatula to 10 ml of the media in a conical flask, while stirring until a heterogeneous system (solid sample and liquid) is obtained. The solution containing excess solid is then capped and stirred at 150 rpm at room temperature for 24 hours. The solution containing excess solid is filtered using 0.45µm PVDF filter, appropriate dilutions are then made and analyzed using UV spectrophotometer at required nanometer range of drug. The same procedure is followed for all selected drugs. (Saturation solubility is carried out at 25°C using required different buffers).

Determination of absorption maximum (λ_{max}):

The wavelength at which maximum absorption of radiation takes place is called as λ_{max} . This λ_{max} is characteristic or unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in ultraviolet region (190-390nm), as they are aromatic or contain double bonds.

Accurately weighed 100mg of drug is dissolved in pH 6.8 buffer taken in a clean 100 ml volumetric flask. The volume is made up to 100ml with the same which will give stock solution-I with concentration 1000µg/ml. From the stock solution I, 5ml is pipette out in 50ml volumetric flask. The volume is made up

to 50ml using pH 6.8 buffer to obtain stock solution-II with a concentration 100µg/ml. From stock solution-II, 1ml is pipette out in 10ml volumetric flask. The volume is made up to 10ml using pH 6.8 buffer to get a concentration of 10µg/ml. This solution is then scanned at 200-400nm in UV-Visible double beam spectrophotometer to attain the absorption maximum (λ_{max}).

PREPARATION OF CALIBRATION CURVE

Procedure for standard curve in pH 6.8: 10 mg of drug is dissolved in 10 ml of pH 6.8 by slight shaking (1000 mcg/ml). 1 ml of this solution is taken and made up to 20 ml with pH 6.8, which gives 20 mcg/ml concentration (stock solution). From the stock solution, concentrations of 5, 10, 15, 20 and 25 µg/ml in pH 6.8 are prepared. The absorbance of dilute solutions is measured at particular nanometer and a standard plot is drawn using the data obtained. The correlation coefficient is calculated.

FTIR analysis: The drug-polymer interactions are studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) is mixed with dry KBr. The mixture is ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc is scanned 10 times at a resolution of 2 cm⁻¹ using Happ-Genzel apodization. The characteristic peaks are recorded.

MICROMERETIC PARAMETERS:

Bulk Density:

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is determined by pouring pre-sieved blend into a graduated cylinder via a large funnel and measure the volume and weight as is given by
Bulk density= weight of blend/Bulk volume

Tapped density:

Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapped apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

Tapped density=weight of blend/tapped volume of blends

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Hausner's ratio: Hausner's ratio is determined as the ratio between the tapped densities to that of the bulk density.

H.R = Tap Density / Bulk Density

Angle of repose: The manner in which stresses are transmitted through a bed and beds response to applied stress is reflected in the various angles of friction and response. The most commonly used of these is angle of repose, which may be determined experimentally by a number of methods. The method used to find the angle of repose is to pour the powder in a conical heap on a level flat surface and measure the inclined angled with the horizontal pile.

$$\theta = \tan^{-1}(h/r)$$

Particle Size It is possible to use ordinary microscope for particle size determination in the range of 0.2 to above 100 μm to measure particle size of individual microsphere. All the microspheres are evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. Ocular micrometer is calibrated with the stage micrometer. Slides of dilute suspensions of microspheres in liquid paraffin are prepared and slides are placed on mechanical stage of microscope. The diameter of 100 microspheres is measured randomly by optical microscope and average particle size is determined.

Scanning electron microscopy (SEM):

In the pharmaceutical industry, SEM may be used as a qualitative tool for the analysis of drug substance and drug product in order to obtain information on the shape and surface structure of the material. SEM plays an important role in the characterization of nanoscale and sub-micron particles. It has been used to determine surface topography, texture and to examine the morphology of fractured or sectioned surfaces. The examination of the surface of polymeric drug delivery systems can provide important information about the porosity and microstructure of device.

Actual drug content and entrapment efficiency:

10 mg of microspheres are accurately weighed and transferred in a 50 ml volumetric flask. Volume is adjusted with 1% SLS and microspheres are dissolved by ultra-sonication for 3 h at 25 $^{\circ}\text{C}$. The samples are filtered through 0.2 μm membrane filter. 5 ml from the sample solution is transferred to 50 ml volumetric flask and volume is adjusted to 50 ml with same medium and absorbance of samples are measured at 288 nm using UV-spectrophotometer. Actual drug content (AC) and encapsulation efficiency (EE) are calculated using following equations. All analyses are carried out in triplicate.

$$\text{AC}(\%) = \frac{C_{\text{act}}}{C_{\text{ms}}} \times 100$$

$$\text{EE}(\%) = \frac{C_{\text{act}}}{C_{\text{the}}} \times 100$$

Where,

C_{act}= Actual Cefaclor content in microspheres

C_{ms}= Weighed quantity of microspheres

C_{the}= Theoretical quantity of Cefaclor in microspheres calculated from the quantity added in the process.

In-vitro Dissolution Studies:

The dissolution test measures the amount of time required for certain percentage of the drug substance in a tablet to go into solution under a specified set of conditions. It describes a step towards physiological availability of the drug substance, but it is not designed to measure the safety or efficacy of the formulation being tested.

RELEASE KINETIC MODELS:

To analyze the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained is fitted in to Zero order, First order, Higuchi matrix, Krosmeysers-Peppas and Hixson Crowell model. In this by comparing the R²-values obtained, the best-fit model is selected.

Stability studies: Stability studies are conducted for the upgrade formulation confirmed from the in vitro dissolution data, for Particle size, % Yield, Entrapment efficiency, & % Drug content at 40 $^{\circ}\text{C}$ /75%RH for a period of 3 months.

RESULTS AND DISCUSSION

Preparation of microspheres:

Microspheres are prepared by solvent evaporation method. Many of the researchers employed with solvent evaporation method due to its simplicity and reproducibility. The solubility of Cefixime, Cefaclor and Cefdinir are very poor in water (0.13mg/ml, 0.52 mg/ml and 0.14mg/ml) and in 0.1N HCl (0.081mg/ml, 0.072mg/ml and 0.020mg/ml) respectively. The solubility of Cefixime, Cefaclor and Cefdinir increased with increase in pH 6.8 of the buffer from 0.89 to 2.15 mg/ml, 0.39 to 1.88 mg/ml and 0.79 to 1.26 mg/ml respectively.

Solvent combination:

Selection of solvent is very important for microspheres preparation. A mixture of ethanol and dichloromethane used for this microsphere's preparation as solvent. Because when dichloromethane used alone the polymer get precipitated rapidly at the time of mixing with water. So ethanol is added to that solvent. During microspheres formation ethanol gets diffused into the water and dichloromethane is evaporated.

Determination of absorption maxima (λ_{max}) of CEFIXIME, CEFACLOR and CEFDINIR:

The maximum absorbance of the Cefixime, Cefaclor and Cefdinir in PH 6.8 is found to be 286nm, 268nm and 282nm respectively as shown in Fig. Hence, the wavelength of 286nm, 268nm and 282nm are selected for analysis of drug in dissolution media.

Standard curve of Cefixime, Cefaclor and Cefdinir:

A linear relationship is observed between concentrations of drug solution in pH 6.8 and absorbance, over the concentration range of 5-25 µg/mL. The coefficient of correlation (R^2) is found to be 0.9990, indicating that the drugs solutions obeying Beer's- Lambert law in the concentration range of 5-25 µg/ml. Hence it is concluded that dissolution samples can be analyzed in 0.1N HCl by measuring absorbance at 286nm, 268nm and 282nm using UV-Visible Spectrophotometer.

FTIR Studies:

The Cefixime and Excipients, Cefaclor and Excipients and Cefdinir and Excipients interactions are studied by comparing the FTIR spectrum of the optimized blend with that of Cefixime, Cefaclor and Cefdinir pure drug as shown in Fig. The comparison study demonstrates that there is no interaction between the drug and other ingredients of the formulation including Excipients such as HPMC, Eudragit and SCMC as shown in Fig, thus revealing compatibility of the selected drug with the excipients.

MICROMERETIC PARAMETERS:

The flow properties of Cefixime F1 to F9 like bulk density, tapped density, compressibility index and Hausner's ratio are found to be 0.384±0.31gm/cc to 0.54±0.024gm/cc, 0.495±0.50gm/cc to 0.67±0.10gm/cc, 11.5±0.31% to 25.84±0.10% and 1.13±0.09 to 1.55±0.02 respectively and for Cefaclor F10 to F18 0.432±0.14gm/cc to 0.520±0.014gm/cc, 0.478±0.88gm/cc to 0.587±0.23gm/cc, 8.77±0.85% to 13.17±0.25% and 1.09±0.30 to 1.15±0.89 respectively and Cefdinir F19 to F27 0.51±0.25gm/cc to 0.59±0.07gm/cc, 0.62±0.62gm/cc to 0.69±0.14gm/cc, 7.936±0.19% to 23.18±0.50% and 1.086±0.56 to 1.301±0.19 respectively. The observed values are within I.P limits and also exhibit good flow character for the improved formulation.

Particle Size:

The particle size of the formulations F1 to F9, F-10 to F-18 and F19-F27 are found to be in the ranges from 102.5±1.3 to 110±2.21 µm, 100.8±1.6 µm to 106.2±1.3 µm and 102.1±1.3 µm to 108.6±1.7 µm respectively.

Scanning electron microscopy analysis (SEM):

The optimized formulations are evaluated for its surface morphology by using Scanning electron microscopy. The outer surface of the microspheres is found to be smooth. The surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. The particle size is found to be 100 µm.

Actual drug content and entrapment efficiency:

The actual drug content of the Cefixime formulations F1 to F9, Cefaclor F10 to F18 and Cefdinir F19 to F27 are found to be in the ranges from 97.46±2.4 to 98.78±1.4, 95.55±1.4 to 99.92±2.67 and 96.89±2.1 to 99.11±2.1 respectively. The Entrapment Efficiency of the Cefixime formulations F1 to F9, Cefaclor F10 to F18 and Cefdinir F19 to F27 are found to be in the ranges from 75.69±1.91 to 88.35±2.67%, 75.72±1.94 to 92.02±1.07% and 75.69±1.91 to 89.45±1.63% respectively.

Invitro dissolution studies of Cefixime, Cefaclor and Cefdinir:

The formulations F1-F3, F10- F12 and F19-F21 prepared with (ratios range 1:1, 1:1.5, 1:2) concentration of polymer like SCMC and drug release as shown in Table. As the polymer concentration decreases the drug release increases. This is due to insufficient entrapment of the drug formulations contain low concentration of hydrophilic polymer (SCMC).

The formulations F1, F10 and F19 showed burst effect. F1 of Cefixime released 98.09±0.23% at the end of 4hrs, F10 of Cefaclor & F19 of Cefdinir released 100.23±0.74% and 100.18±0.18 at the end of 6hrs.respectively. F2 & F3 of Cefixime released 99.84±0.6%, 99.85±0.7 at the end of 6 and 10hrs respectively. F11 and F12 of Cefaclor and F20 and F21 of Cefdinir released 99.46±0.30%, 97.73±0.70 and 98.98±0.59, 99.23±0.50% at the end of 8 and 10 hrs respectively, due to increase of the polymer concentration. Increase of polymer concentration in formulations F3, F12 & F21 (1:2 ratio) drug release is decreased.

The formulations of Cefixime F4, F5 releases 98.81±0.78, 95.41±0.07 at the end of 10hrs. Formulation of Cefixime F6 releases 97.87±0.22 at the end of 12hrs. F13 formulation of Cefaclor and F22 formulation of Cefdinir releases 99.23±0.64 and 99.85±0.79% at the end of 8 hrs and 6hrs respectively. A formulation of Cefaclor F14 and F15 releases 98.45±0.47% & 80.45±0.87 at the end of 12hrs. F23 & F24 Formulation of Cefdinir released 99.87±0.36% & 89.99±0.48 at the end of 12hrs. Because the HPMC (high viscosity and high molecular weight) upon contact with dissolution medium swelling occur due to the disruption of hydrogen bonding among the polymeric chains and form a thick gel layer on the surface, which gets eroded over period of time. Thus, this parameter is responsible for sustained/controlled drug release rate.

The formulations of Cefixime (F7-F9), Cefaclor (F16-F18) and Cefdinir (F25-F27) are tried with Eudragit (ratios range 1:1, 1:1.5, 1:2) as retardant being insoluble in gastric pH. The formulations F7 and F16

and F25 are found to be 100.14 ± 0.49 at the end of 10hrs and 82.45 ± 0.65 and 70.89 ± 0.15 at the end of 12hrs respectively due to low polymer concentration effect. F8, F9 of Cefixime, F17, F18 of Cefaclor and F26, F27 of Cefdinir showed better control on drug release than other formulations and also exhibited incomplete drug release which might be due to hydrophobic polymer (Table and Fig).

The formulation of Cefixime F6 (drug: HPMC 1:2), Cefaclor F14 (drug: HPMC 1:1.5) and Cefdinir F23 (drug: HPMC 1:1.5) are made with the HPMC in the drug polymer ratio drug releases are found to be 97.87 ± 0.22 , 98.45 ± 0.47 and 99.87 ± 0.36 % at the end of 12hrs with better drug release pattern. The reason for this is the formation of thick gel layer by matrices around the surface that delays diffusion and release of drug, thus F6 formulation of Cefixime and Cefaclor formulation F14 and formulation of Cefdinir F23 are considered as optimized formulations.

RELEASE KINETIC MODELS:

The optimized formulations of Cefixime F6, Cefaclor F14 and Cefdinir F23 have coefficient of determination (R^2) values of Zero order, First order, Higuchi and Korsmeyer Peppas of 0.9560, 0.7870, 0.9820 and 0.9920 respectively and for Cefaclor 0.954, 0.764, 0.977 and 0.959 respectively and for Cefdinir 0.874, 0.931, 0.971 and 0.964 respectively. A good linearity is observed with the zero order for Cefixime F6 and F14 Cefaclor formulations. For F23 formulation of Cefdinir first order. The slope of the regression line from the Higuchi plot indicates the rate of drug release through mode of diffusion, and further confirms the diffusion mechanism. The data fitted into the Korsmeyer Peppas equation which showed linearity with slope n value of Cefixime for optimized formulation F6 is 0.5980, 0.493 for optimized formulation of Cefaclor F14 and 0.515 for optimized formulation of Cefdinir. This n value

indicates the coupling of (swelling, polymer relaxation) diffusion and erosion mechanism. This type of drug release is called as anomalous diffusion. Thus, it indicates the drug release from the tablet follows non-Fickian diffusion mechanism. The presence of swelling and cross-linked polymers within the matrix structure might be responsible for the drug release controlled by more than one process. Thus, with regards to release kinetics, the optimized batch F6 and F14 follows best fits into peppas model and shows zero order F23 follows peppas model and shows first order and drug release with non-Fickian diffusion mechanism.

Stability studies of optimized formulation F6, F14 and F23:

Stability studies are conducted for Particle size, % Yield, Entrapment efficiency, & % Drug content and confirmed that there is no significant change in the parameters of optimized formulation at storage condition of $40^\circ\text{C} \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$ after 6 months.

CONCLUSION:

In this research work attempt is made to increase the bioavailability of the Cefixime and Cefaclor with reducing dosage frequency microspheres. Formulation is successfully made and in –vitro evaluation shows encouraging results. By these evaluations following statement can be concluded (i) No interaction between the drug and polymer was confirmed. (ii) The desired yield and entrapment efficiency was obtained. (iii) It provides sustained release of drug over more than 12 hours. (iv) Drug release from microspheres follows zero order and first order drug release with non-Fickian diffusion mechanism. (v) The drug: polymer ratio has significant effect on the all characteristics of microspheres, but other variables have effect on only few characteristics of the microspheres.

Table 1: Formulation design of Cefixime, Cefaclor and Cefdinir Microspheres:

Ingredients	F1/ F10/ F19	F2/ F11 /F20	F3/ F12/ F21	F4/ F13/ F22	F5/ F14 /F23	F6/ F15/ F24	F7/ F16/ F25	F8/ F17/ F26	F9/ F18/ F27
Cefixime/ Cefaclor/ Cefdinir gm	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
SCMC gm	1	1.5	2	---	---	---	---	---	---
HPMCK4M gm	---	---	---	1	1.5	2	---	---	---
EUDRAGIT gm	---	---	---	---	---	---	1	1.5	2
Ethanol ml	6	10	12	15	20	23	10	15	20
DCM ml	6	10	12	15	20	23	10	15	20
Tween ml	0.18	0 .18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Liquid Paraffin ml	90	90	90	90	90	90	90	90	90

Table: 2 Characterization of Cefixime, Cefaclor and Cefdinir Microspheres

Formulations Cefixime/ Cefaclor/ Cefdinir	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility Index
F1/	0.454±0.12	0.526±0.14	1.55±0.02	13.64±0.01
F10/	0.516±0.55	0.587±0.23	1.13±0.16	12.09±0.47
F19	0.57±0.14	0.63±0.07	1.105±0.01	9.523±0.75
F2/	0.411±0.05	0.524±0.32	1.27±0.09	21.40±0.21
F11/	0.520±0.14	0.57±0.66	1.09±0.30	08.77±0.85
F20	0.53±0.78	0.64±0.12	1.207±0.15	17.18±0.48
F3/	0.397±0.12	0.497±0.14	1.25±0.07	20.04±0.21
F12/	0.487±0.58	0.546±0.50	1.12±0.07	10.80±0.21
F21	0.51±0.25	0.62±0.62	1.215±0.36	17.74±0.89
F4/	0.416±0.32	0.495±0.5	1.18±0.19	11.5±0.31
F13/	0.455±0.25	0.501±0.44	1.10±0.60	9.18±0.14
F22	0.54±0.09	0.68±0.71	1.259±0.78	22.58±0.56
F5/	0.429±0.09	0.542±0.21	1.27±0.12	20.97±0.09
F14/	0.448±0.78	0.516±0.36	1.15±0.89	13.17±0.25
F23	0.52±0.63	0.64±0.33	1.230±0.41	18.75±0.78
F6/	0.49±0.08	0.64±0.1	1.30±0.04	23.4±0.08
F15/	0.510±0.07	0.568±0.14	1.11±0.55	10.21±0.61
F24	0.58±0.69	0.63±0.45	1.086±0.56	7.936±0.19
F7/	0.409±0.10	0.552±0.09	1.34±0.12	25.84±0.10
F16/	0.476±0.15	0.526±0.22	1.10±0.23	9.50±0.55
F25	0.53±0.57	0.69±0.14	1.301±0.19	23.18±0.51
F8/	0.54±0.024	0.67±0.10	1.24±0.10	19.4±0.11
F17/	0.515±0.66	0.570±0.01	1.10±0.08	9.64±0.14
F26	0.59±0.07	0.67±0.30	1.135±0.02	19.40±0.41
F9/	0.384±0.31	0.50±0.12	1.13±0.09	23.08±0.09
F18/	0.432±0.14	0.478±0.88	1.10±0.12	9.62±0.05
F27	0.55±0.10	0.66±0.21	1.2±0.11	16.66±0.05

Table: 3 Particle size, Drug Content and Entrapment Efficiency of Cefixime, Cefaclor and Cefdinir Microspheres

Formulations Cefixime/ Cefaclor/ Cefdinir	Particle Size	Percentage Yield	Entrapment Efficiency	Drug Content
F1/	106.5±2.3	93.70±1.28	87.04±1.92	98.56±0.63
F10/	102.1±1.3	87.82±2.01	78.68±2.1	97.65±1.6
F19	103.4±1.42	92.70±1.19	85.04±1.87	97.59±1.97
F2/	110±2.21	87.82±2.01	78.68±2.1	98.48±0.91
F11/	102.9±1.4	85.95±1.98	76.87±1.91	96.89±2.1
F20	102.5±1.3	85.95±1.98	76.87±1.91	98.64±2.01
F3/	103.4±1.42	92.70±1.19	85.04±1.87	97.59±1.97
F12/	101.9±1.7	94.82±2.16	88.35±2.67	98.28±1.7
F21	103.2±0.9	94.82±2.16	89.45±1.63	98.46±3.22
F4/	102.5±1.3	85.95±1.98	76.87±1.91	98.64±2.01
F13/	104.2±1.2	86.90±2.45	75.72±1.94	98.73±1.9
F22	103±2.8	86.90±3.05	75.69±1.91	98.78±1.4
F5/	103.2±0.9	94.82±2.16	88.35±2.67	98.46±3.22
F14/	105.1±1.5	93.55±1.37	86.68±2.08	97.89±1.92
F23	108.6±1.7	93.25±1.37	86.98±2.08	99.11±2.1
F6/	103.0±2.8	86.90±3.05	86.98±2.08	98.78±1.4

F15/	106.2±1.3	85.35±1.98	76.84±1.98	98.48±2.08
F24	106±2.35	84.62±1.01	76.68±2.1	97.46±2.4
F7/	108.6±1.7	93.25±1.37	75.69±1.91	99.11±2.1
F16/	101.8±1.1	86.27±2.05	76.68±2.12	99.24±1.91
F25	103.8±1.8	93.70±1.28	87.04±1.92	98.95±1.8
F8/	106±2.35	85.82±2.01	76.68±2.1	97.46±2.4
F17/	100.8±1.6	98.70±1.87	92.02±1.07	99.92±2.67
F26	102.1±1.3	87.82±2.01	78.68±2.1	97.75±1.5
F9/	103.8±1.8	93.70±1.28	87.04±1.92	98.95±1.8
F18/	101.1±1.1	85.82±2.01	88.68±1.1	95.55±1.4
F27	102.9±1.4	85.95±1.98	76.87±1.91	96.89±2.1

Table4: Dissolution profile of CEFIXIME (F1-F9), CEFACLOX (F10-F18) and CEFDINIR (F19-F27) formulations (Mean±SD; n=6)

Intervals(hr)	0	1	2	4	6	8	10	12
F1	0	42.45±0.47	72.45±0.54	98.09±0.23	***	***	***	***
F10	0	38.82±0.71	63.45±0.45	84.46±0.41	100.23±0.74	***	***	***
F19	0	40.85±0.56	71.35±0.46	91.52±0.57	100.18±0.18	***	***	***
F2	0	35.35±0.89	68.85±0.87	82.85±0.56	99.84±0.6	***	***	***
F11	0	30.23±0.40	54.23±0.36	70.63±0.12	81.23±0.55	99.46±0.30	***	***
F20	0	33.32±0.30	57.53±0.18	73.85±0.42	85.85±0.07	98.98±0.57	***	***
F3	0	28.45±0.36	48.92±0.54	62.45±0.67	78.58±0.59	89.23±0.65	99.85±0.7	***
F12	0	28.89±0.14	38.23±0.33	49.99±0.52	68.89±0.74	83.45±0.02	97.73±0.70	***
F21	0	26.89±0.91	49.85±0.87	67.23±0.79	79.99±0.63	84.55±0.42	99.23±0.51	***
F4	0	32.84±0.15	44.85±0.43	59.98±0.26	70.23±0.75	86.55±0.10	98.81±0.78	***
F13	0	35.69±0.12	50.23±0.05	67.74±0.47	82.12±0.59	99.23±0.64	***	***
F22	0	38.91±0.14	64.85±0.36	86.35±0.45	99.85±0.79	***	***	***
F5	0	29.98±0.44	39.45±0.51	47.42±0.78	62.45±0.30	79.98±0.19	95.41±0.07	***
F14	0	28.23±0.34	36.53±0.54	43.45±0.10	59.53±0.06	71.25±0.40	83.45±0.20	98.45±0.47
F23	0	25.12±0.02	39.42±0.79	46.8±0.58	55.23±0.36	69.98±0.47	85.54±0.28	99.87±0.36
F6	0	20.25±0.77	33.46±0.15	45.55±0.09	58.88±0.48	69.89±0.70	79.54±0.36	97.87±0.22
F15	0	15.23±0.10	28.23±0.22	39.42±0.84	48.86±0.74	60.99±0.65	73.45±0.02	80.45±0.87
F24	0	19.87±0.18	30.24±0.55	44.89±0.17	58.87±0.45	67.54±0.32	79.86±0.14	89.99±0.48
F7	0	20.23±0.17	29.85±0.55	50.25±0.33	78.89±0.60	89.95±0.74	100.14±0.49	***
F16	0	20.12±0.49	32.43±0.12	44.52±0.30	51.23±0.78	63.33±0.04	75.23±0.25	82.45±0.65
F25	0	10.53±0.65	19.83±0.49	25.35±0.87	37.45±0.96	42.54±0.74	58.87±0.58	70.89±0.15
F8	0	14.45±0.58	20.89±0.70	29.85±0.21	48.88±0.56	54.85±0.61	62.85±0.31	69.85±0.05
F17	0	13.35±0.10	18.54±0.45	27.84±0.36	45.57±0.71	53.84±0.05	59.99±0.89	65.54±0.70
F26	0	8.45±0.19	15.45±0.97	21.23±0.56	32.35±0.39	39.01±0.47	50.08±0.52	62.15±0.87
F9	0	11.52±0.41	15.23±0.30	25.32±0.55	30.51±0.21	38.54±0.02	45.23±0.09	51.21±0.10
F18	0	12.21±0.82	18.15±0.09	24.23±0.79	29.47±0.56	38.89±0.34	49.98±0.10	59.98±0.54
F27	0	7.23±0.09	14.18±0.57	19.98±0.18	27.46±0.96	32.24±0.87	46.64±0.11	57.98±0.89

Table 5: Co-efficient of determination and 'n' values of optimized formulations F6, F14 and F23

Formulations	R ² Value		n Value		
	Zero order	First order	Highuchi	Korsmeyer Peppas	Korsmeyer Peppas
CEFIXIME F6	0.9650	0.7870	0.9820	0.9920	0.5980
CEFACLOX F14	0.9540	0.7640	0.9770	0.9590	0.4930
CEFDINIR F23	0.8740	0.9310	0.9710	0.9640	0.515

Table 6: Stability data of Cefixime, Cefaclor and Cefdinir optimized formulations (F6), (F14) and (F23) physico-chemical parameters

Parameter	Particle Size	% Yield	Entrapment Efficiency	% Drug Content
Initial for Cefixime F6	103±2.8	86.90±3.05	86.98±2.08	98.78±1.4
For F6 After 3months at 40° C/75%RH	102.47±2.2	86.81±2.89	86.87±1.87	98.70±1.05
For F6 After 6months at 40° C/75%RH	102.89±2.55	86.92±3.11	86.94±2.01	98.76±1.33
Initial for Cefaclor F14	105.1±1.5	93.55±1.37	86.68±2.08	97.89±1.92
For F14 After 3months at 40° C/75%RH	105.20±0.87	93.47±1.08	86.50±2.41	97.74±1.08
For F14 After 6months at 40° C/75%RH	105.12±1.8	93.45±1.20	86.79±1.56	97.92±1.54
Initial for Cefdinir F23	108.6±1.7	93.25±1.37	86.98±2.08	99.11±1.57
For F23 After 3months at 40° C/75%RH	108.45±1.06	93.14±1.01	86.56±1.89	99.09±1.04
For F23 After 6months at 40° C/75%RH	108.3±1.23	93.21±1.41	86.90±2.01	99.03±1.78

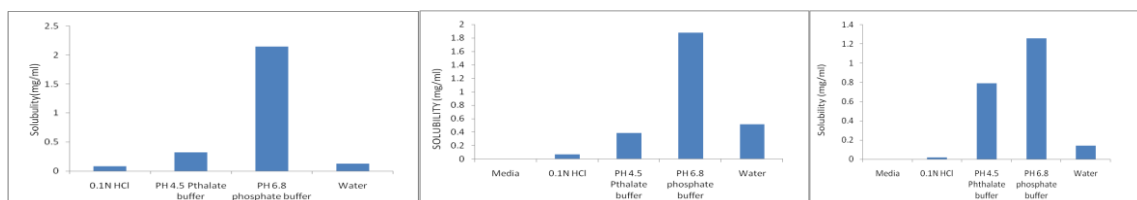


Fig1: Saturation solubility of CEFIXIME, CEFACTOR and CEFDINIR

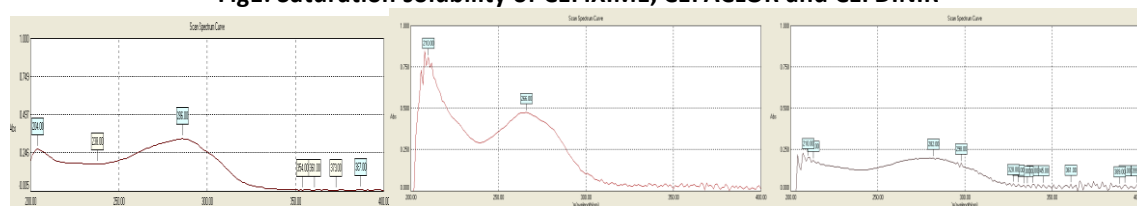


Fig2: Determination of absorption maxima of Cefixime, Cefaclor and Cefdinir

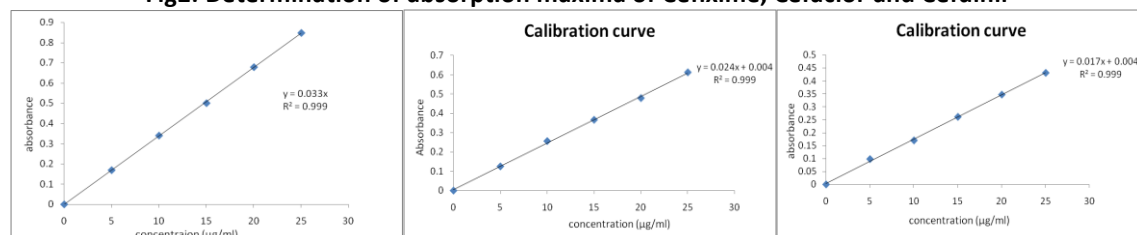


Fig3: Standard curve of CEFIXIME, CEFACTOR and CEFDINIR in pH 6.8(λ_{max} 286, 268 and 282nm)

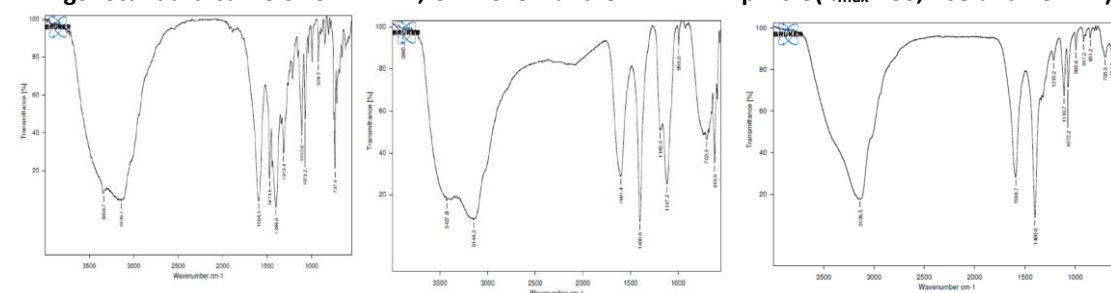


Fig 4: FTIR of CEFIXIME, CEFACTOR and CEFDINIR

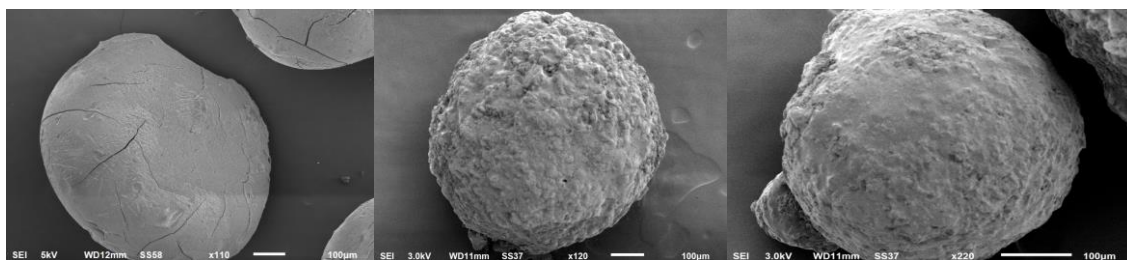


Fig.5: SEM analysis of CEFIXIME, CEFACTOR and CEFDINIR

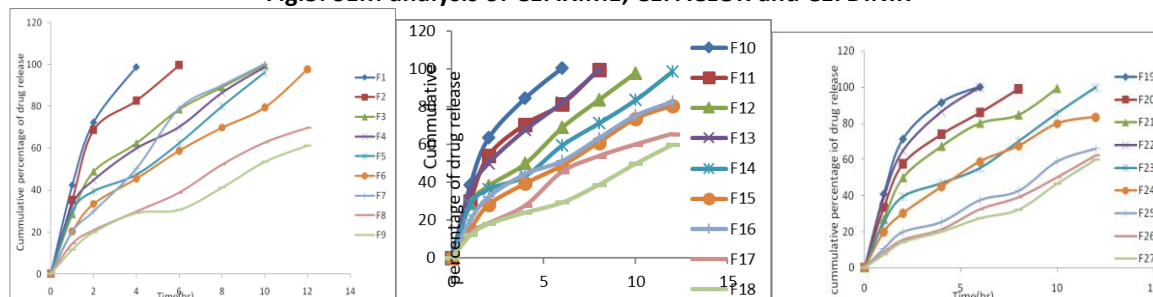


Fig 6: In-vitro dissolution profile of CEFIXIME, CEFACTOR and CEFDINIR

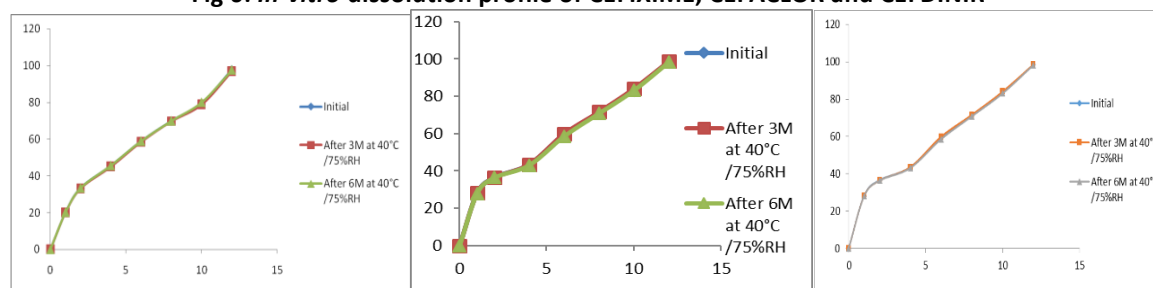


Fig 7: Optimized formulation of CEFIXIME (F6), CEFACTOR (F14) and CEFDINIR (F23) in-vitro dissolution at 40°C /75%RH

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