IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

DEVELOPMENT AND CHARACTERIZATION OF CIPROFLOXACIN MICROSPHERES AS SUSTAINED RELEASE DOSAGE FORM

[1]Neha Ahirwar, [2]Dr. Anjita Singh, [3]Dr. Jagdish rathi

[1,2,3]NRI Institute of Pharmaceutical Sciences, Bhopal

ABSTRACT: The main objective is development and characterization of ciprofloxacin microsphres as sustained release dosage form. Preformulation study was carried out initially and Drug (Ciprofloxacin) was identified by different methods. UV spectrophotometric study, FTIR spectra and was performed for the authentication of the drug. The λmax was found to be 276.0 nm and comparison with literature value authenticates the study. Calibration curve of the drug was prepared. The absorbance was measured at 276.0 nm against a blank solution using UV-Visible spectrophotometer. Linearity was observed with an $R^2 = 0.998$ in 0.1N HCL at 276.0 nm.The drug-Exciepients compatibility studies using FT-IR and indicated no interaction between the drug and polymers. The microspheres prepared by two different technique for using synthetic polymer and natural polymer utilizing temperature change showed a good specificity, with smooth surface and the particles are distributed uniformly without any lumps. In synthetic polymer (Ethyl cellulose) prepared by solvent evaporation technique and natural polymer (guar gum) ionic cross linking technique. Scanning electron microscopy for the optimized formulation for natural and synthetic shown in fig. 7.8 and 7.7. The particle size is formulated batches of microspheres were shown in table No.7.9. The particle size distribution was uniform and narrow. The release profile of microspheres was studied for first two hours in stimulated gastric pH using 0.1N hydrochloric acid. The percent of drug release was calculated by adding the amount of drug released at the end of 2^{nd} hour in stimulated gastric pH to the amount of drug released in stimulated intestinal pH. The whole release study data was given (Table: 7.10 and 7.11). As the compare of EC and Guar gum release the best sustained effect over a period of 24 hours and ethyl cellulose microsphere was 97.913 % of the drug was released at the end of 24 hours.

KEYWORDS: Dosage form, Evaluation, Dissolution, Compression, Sustained release.

INTRODUCTION: For any drug therapy to be successful the drug must reach the target tissue or systemic circulation in optimum concentration which should be maintained for desired time. Therapeutic response of the drug also depends on the pharmacokinetics of the drug in an individual patient and frequency of dosing. Many acute and chronic diseases require frequent medication. Drug with short half life also require frequent dosing, some problem may be arises like patient noncompliance to the prescribed drug regimen, particularly in case of chronic treatment or in the treatment of a silent disease such as arthritis.

As the drug needs to be given repeatedly, there may be accumulation which leads to toxicity. In such circumstances, the problem can be solved by developing new drugs or dosage from like prolonged release dosage form with similar therapeutics response as that of conventional dosage forms and longer duration of action.[1]

For last so many decades conventional dosage forms, like tablets, capsules, pills, powders, parental preparations, solutions, emulsions, suspensions, creams, ointments and aerosols are used in the treatment of acute or chronic diseases. Even today these formulations can be considered as primary pharmaceutical product commonly seen in market. When such a conventional dosage form is administrated, the concentration of such drug in systemic circulation gradually rises to attend a therapeutic range and this concentration is maintained for some time and finally decreases to sub therapeutic value rendering the drug pharmacological inactive.

Ideally the drug concentration should be continuously maintained within therapeutic level. However, for drug with short half life, it is not possible to maintain the drug concentration within therapeutic range without frequent dosing. However frequent dosing may lead to patient noncompliance and drug toxicity and hence the desirable solution is sustained release products.

Although earlier literature shows some reference to oral SR preparation, the first practical product of this category is the “Dexedrine” capsule which was marketed in Oct. 1952. During year 1935-50 sustained release products appeared as a new drug delivery in pharmaceutical field. Since 1960 much attention has been focused on SR preparation. Since that time a number of strategies have been developed. The work is much extensive and has been reviewed by several authors time to time. These reviews provide detailed information about clinical evaluations and performance. The strategies range from the very simple slowly dissolving tablets or pellets to the technically more sophisticated controlled drug release systems.The objective of any drug delivery system is to provide drug in therapeutic amount to the proper site in the body to achieve immediately and then maintain the desired drug concentration. These idealized objectives are achieved by appropriately developed SR drug deliveries which also have diverse applicability and merits.

The sustained drug delivery includes the application of physical and polymer chemistry. These polymers slowly release the drug in bio-system and maintain drug blood level within therapeutic range for longer duration. Some of the products characterize the drug permeation through the appropriate biological membrane and any first pass metabolic effects prior to the entry of drug into systemic circulation. The fact that the absorption and release rate of the drug from the dosage form, is one of the interesting and most recent development in pharmaceutical field.

Oral route is most convenient and commonly employed route of drug administration. The oral route of administration for sustained release products has by far received major attention with respect to research on physiological drug constrains as well as design and testing of products. The route has gained importance because of the technological advance which helps to achieve zero order release rates of the drug and low cost etc.[2]

In the past, many of the terms describing sustained release formulation have been used in confusing and inconsistent manner. Therefore it is necessary to give a short explanation of the terminology involved. Various terms such as smart, slow release, controlled release targeted release, gradual release, long lasting, protracted release, time release; extended action, repeat action, depot formulation, repository, intelligent, therapeutics and spaced release etc.

Long acting dosage forms can be broadly classified into the following classes:-

- Sustained release

Indicate an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.

- Prolonged release

Dosage form release drug slowly, so that plasma concentration are maintained at therapeutic level for a prolonged period of time (usually to 12 hours).

- Controlled release

Dosage form release drug at a constant rate and provide plasma concentration that remain invariant with time.

- Delayed release

Indicate that the drug is not released immediately following administration, but at an altered time e.g. enteric coated tablet.

- Repeat action

Indicate that an individual dose is released fairly soon after administration, and second or third dose are subsequently released at intermittent intervals.

- Modified release

Dosage form are defined by USP as the those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objective not offered by conventional form.[3]

MATERIALS AND METHODOLOGY

Materials Used

All the materials used were of analytical grade.

Table 1: List of Materials used

Sr.No.	Materials used	Manufacturer
1	Ciprofloxacin	Zee Laboratory, Konta Saheb, H.P.
2	Ethyl cellulose	Oxford Laboratory, Mumbai
3	Ethanol (95%)	Jiangsu Huaxi International Trade co.Ltd.China
4	Guar gum	Titan Biotech Limited,Bhiwadi
5	Heavy liquid paraffin	Hemedia Laboratory Pvt Ltd.,Mumbai
7	Tween 80	J & k scientific ltd.China
8	N-Hexane	Loba Chemte pvt,Ltd.,Mumbai
9	Sodium Alginate	Oxford Laboratory, Mumbai
10	$CaCl_2$	Oxford Laboratory, Mumbai

Equipments Used

Table 2: List of Materials Used

Sr.No.	Equipments / Instruments	Manufacturer
1	Ultra sonicator	EI Instrument,Ahemdabad
2	FT-IR	Brukar Optics, Germany
3	Hot Air Oven	Khera Instrument, New Delhi
4	Melting Point Apparatus	E.I. Instrument, Ahmadabad
5	Mechanical Stirrer	Remi, Bombay
6	Optical Microscope	Lyzer, Ambala, Hariyana
7	Digital pH Meter	Shimadzu, Japan.
8	Digital Weighing Balance	Shimadzu, Japan.
9	UVSpectrophotometer	UV-1800,Shimadzu,Japan
10	Auto fine coater-JFC 1600	JEOL
11	Analytical SEM-JSM-6390A	JEOL

Method

Preformulation Study

Organoleptic Properties

The drug (Ciprofloxacin) powder was examined for its organoleptic properties like color, odor and taste it was observed that.

Solubility Estimation

The sample was qualitatively tested for its solubility in various solvents. It was determined by taking 10 mg of drug sample in 10 ml of solvent as water, methanol, ethanol, 0.1N HCL, pH buffer 6.8 and buffer pH 7.4 in test tubes and well solubilized by shaking, according to IP. Various solubility terms as is shown in Table 7.2.

Table 3: Various Solubility Terms [44]

Descriptive Term	Parts of Solvent Required For Parts of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble or insoluble	10,000 more

Melting Point Determination

The Melting point was determined by the capillary method using Digital Melting point apparatus. The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.

Preparation of Calibration Curves (by using UV method)

Ciprofloxacin solution was scanned in the U.V. range of 200-400 nm using UV-1800 Shimadzu, Double beam visible spectrophotometer.

Determination of Wavelength of Maximum Absorbance (λ_{max})

- **Preparation of Stock Solution**

10 mg of drug was weighed accurately and transferred to 10 ml of volumetric flask. Then 10 ml solvent was added to dissolve the drug completely. The prepared solution was 1000 µg / ml. 1 ml of above solution was then transferred to another 10 ml volumetric flask and diluted it up-to the mark with solvent. This was 100

µg / ml, and then 1 ml solution was taken from the above solution and again diluted up to 10 ml it gives 10 µg / ml solution. From this solution further dilutions were prepared.

Determination of Partition Coefficient

In chemistry and the pharmaceutical sciences, a partition (P) or distribution coefficient (D) is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium. The terms "gas/liquid partition coefficient" and "air/water partition coefficient" are sometimes used for dimensionless forms of the Henry's law constant. Hence these coefficients are a measure of differential solubility of the compound between these two solvents. The phrase "Partition Coefficient" is now considered obsolete by IUPAC, and "partition constant," "partition ratio," or “distribution ratio," is all more appropriate terms that should be used.

50 mg of drug was weighed accurately and transfer to the separating funnel. The separating funnel was shaken with distilled water and octanol for 2 hrs in a wrist action shaker for equilibration. Two phases was separated and the amount of the drug in aqueous phase was analyzed spectrophotometrically. The partition coefficient of the drug in phases was calculated by using formula.

$$\log P_{oct/wat} = \log \left(\frac{[solute]_{octanol}}{[solute]^{un-ionized}_{water}} \right)$$

Fourier-Transform Infra Red spectroscopy (FTIR)

FT-IR Spectroscopy can be used to investigate and predict any physicochemical interactions between different components, in a formulation and therefore it can be applied to selection of suitable chemically compatible exciepients. While selecting the ingredients, we would choose those which are stable, compatible and therapeutically acceptable. The aim of compatibility study was to test, whether there is any interaction between the exciepients and the drug and compatibility between the drug and exciepients.

Levels of Investigation

IR Spectrum (1) = Pure drug (Ciprofloxacin)
IR Spectrum (2) = Guar gum (Natural Polymer)
IR Spectrum (3) = Ethyl Cellulose (Synthetic Polymer)
IR Spectrum (4) = Ciprofloxacin + Guar gum +Ethyl Cellulose

The IR spectrum of drug substance was authenticated using IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted.

Method of Preparation of Microspheres

Synthetic Polymer

Solvent Evaporation Method [45]

Ciprofloxacin microspheres were prepared by solvent evaporation technique. Polymer like Ethyl cellulose (EC) was dissolved in ethanol. Ciprofloxacin was powdered and dispersed in polymer solution. This solution was added slowly to a beaker containing 300 ml of heavy liquid paraffin (40:60 w/w) and 1% w/w tween80 under constant stirring (600 RPM). After evaporation of ethanol, the microspheres formed were collected by filtration in vacuum, washed 3-4 times with 50 ml of n-hexane each and dried at room temperature for one day. Compositions of various formulations are shown in Table.

Table 4: Compositions of Various Formulations using Ethyl Cellulose

Formulation Code	Ciprofloxacin (mg)	Ethyl Cellulose (mg)	Tween 80 (%W/W)
EC1	100	100	0.01
EC2	100	200	0.01
EC3	100	400	0.01

Natural Polymer

Ionic Cross-Linking Method

The microspheres were prepared by ionic cross-linking technique. The alginate solution comprising 2.5% sodium alginate, 0.25-0.75% hydrophilic polymer and 100 mg of drug were prepared by initially dissolving the polymer in 50% distilled water using gentle heat. On complete dissolution the weighed quantity of drug was add mixed thoroughly in to this solution of sodium alginate was added to afford homogeneous dispersion. The dispersion was added drop wise via 20 gauge hypodermic needle fitted with a 10 ml syringe into 50 ml 5% w/v of cross linking agent (Calcium chloride) solution, being stirred at 200 rpm for 10min. The droplets from the dispersion instantaneously gelled into discrete drug-polymer-alginate matrices upon contact with the solution of cross-linking agent. The formed microspheres were further allowed to stir in the solution of cross-linking agent for an additional of 2 hrs. On expiration, cross-linking agent was decanted and microspheres were washed with 3 x 50 ml volume of distilled water. The microspheres were there after dried at room temperature. Compositions of various formulations are shown in Table 6.5.

Table 5: Compositions of various Formulations using Guar Gum[46]

Formulation Code	Ciprofloxacin (mg)	Sodium Alginate (% w/v)	Guar Gum (% w/v)	Calcium Chloride (% w/v)
G1	100	2.5	0.25	5
G2	100	2.5	0.50	5
G3	100	2.5	0.75	5

Evaluation of Ciprofloxacin Microsphere

Percentage Yield

The yield of microspheres was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug. [47]

$$\text{Percentage yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer used}} \text{ X (100)}$$

Particle Size Analysis

The size of the prepared microspheres was measured by the optical microscopy method using a calibrated stage micrometer. The average size of 100 particles was determined. [47]

Entrapment Efficiency

Ciprofloxacin microsphere was digested in 100 ml distilled water. The suspension was then warmed for a few minutes, filtered & 1 ml of filtrate was made up to 10 ml with distilled water. The solution was analyzed at 276.0 nm to determine amount of ciprofloxacin entrapped in microspheres. [47]

Morphological Characterization of Microspheres

Scanning Electron Microscope (SEM)

The surface morphology of microspheres was investigated using scanning electron microscopy (SEM) by mounting on stubs using double-sided adhesive tapes. The stubs were then vacuum-coated with gold-palladium alloy using coat sputter JFC 1600 (JEOL, Japan) and the microspheres were observed and examined using SEM (JEOL JSM 6390 A).[22]

In-Vitro Release Studies

In- vitro release studies were carried out using USP type I apparatus at 37 ± 0.5ºC in 900 ml of 0.1N HCL for 24 h. Microspheres equivalent to 20 mg drug was placed into the baskets (tied using muslin cloth), and rotated at 100 rpm.5 ml sample was withdrawn at various time intervals like 0, 1, 2, 4, 6, 8, 10, 12 and 24 h and filtered, analyzed by UV spectrophotometrically at 276.0 nm using UV-1800, Shimadzu.

RESULT AND DISCUSSION

Pre-formulation

Identification of Drug

- **Organoleptic Properties**

The organoleptic properties of drug are shown in table 7.1

Table 1: Organoleptic Properties of Drug

Test	Specification / Limits	Observations
Color	Faintly yellowish to light yellow crystalline substance	Yellowish crystalline powder
Taste	Bitter	Bitter
Odor	Odorless	Odorless

Solubility

The sample was qualitatively tested for its solubility in various solvents. It was determined by taking 2 mg of drug sample in 5 ml of solvent as water, methanol, ethanol, ethyl acetate etc., in small test tube and well solubilized by shaking. Solubility study in different solvents at room temperature revealed that it is soluble in water, 0.1N HCL, Very slightly soluble in methanol and ethanol, Slightly soluble in acetone, Simulated gastric fluid (pH 1.2) and phosphate buffer saline (pH 7.4) and insoluble in 0.1N NaOH and chloroform. Solubility profile of Ciprofloxacin is shown in table.

Table 2: Solubility Profile of Ciprofloxacin

Sr. No.	Medium	Solubility Profile	Parts of Solvent
1	Distilled water	Freely soluble	1 – 10
2	Acetone	Slightly Soluble	100 -1000
3	Ethanol	Freely soluble	1 – 10
4	Ethyl acetate	Freely Soluble	1 – 10
5	0.1N HCL	Freely soluble	1-10
6	0.1N NaOH	Freely Soluble	1-10
7	Phosphate Buffer Saline (pH 7.4)	Slightly Soluble	100 – 1000

Freely soluble = 1 -10 parts of solvent, soluble = 10 -30 parts of solvent, sparingly soluble = 30 -10 parts of solvents, slightly soluble = 100 -1000 parts solvent, very slightly soluble = 1000 – 10000 parts of solvent.

Melting Point

The Melting point of drug is shown in table 3.

Table 3: Melting Point of Drug

Material	Specification	Observation
Ciprofloxacin	255 - 257 ^{0}C	253-255^{0}c

Determination of Wavelength of Maximum Absorbance (λ_{max})

Ciprofloxacin solution was scanned in the U.V. range of 200-400 nm using UV Visible spectrophotometer (Shimadzu). The spectrophotometric method of analysis of Ciprofloxacin at λ_{max} 276.0 nm was found to be reproducible and highly sensitive. The standard curves of Ciprofloxacin were prepared in distilled water and 0.1N HCL, at λmax 276.0 nm. The data were regressed to obtain the straight line. The correlation coefficient greater than 0.99 was observed in all the cases, which indicated that, the drug follows Beer-Lambert's law in the concentration range of 5-30 µg/ml.

Table 4: The wavelength of Maximum Absorbance (λ_{max}) of Ciprofloxacin

Conc. (µg/ml)	Scanning Range(nm)	Highest Peak(λ_{max})nm
10	200 – 400	276.0

Calibration Curve of Ciprofloxacin using Distilled Water

The calibration curve was plotted between the concentration and absorbance. The calibration curve of 5-30µg/ml was carried out. The slope and intercept of the calibration curve were 0.018 and 0.005 respectively. The correlation coefficient 'r^2' values were calculated as 0.998.

Table 5: Calibration Curve of Ciprofloxacin in Distilled Water

Sr. No.	Concentration(µg/ml)	Absorbance at 276.0nm
1	0	0
2	5	0.102
3	10	0.185
4	15	0.285
5	20	0.369
6	25	0.476
7.	30	0.545

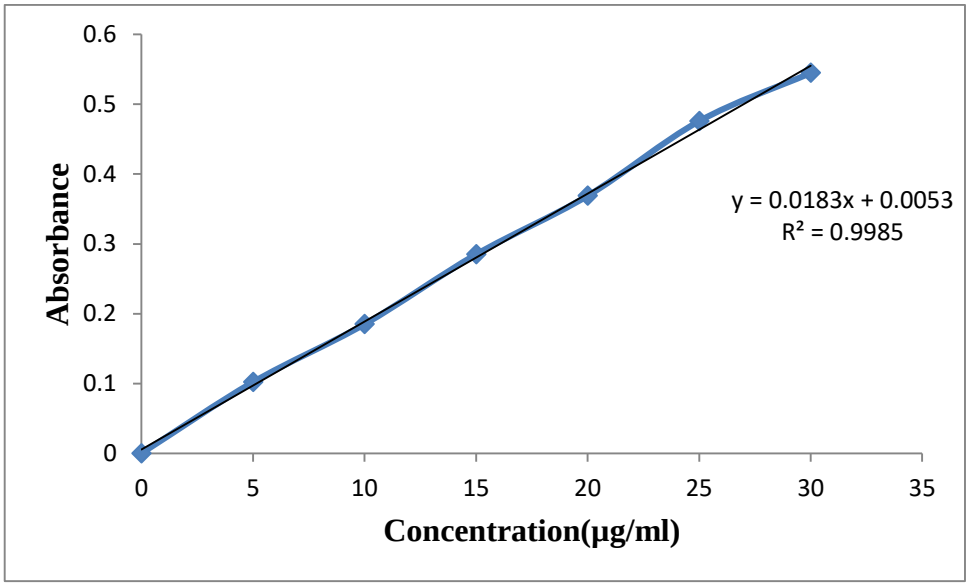

Fig 1: Calibration curve of Ciprofloxacin in Distilled water

Calibration Curve of Ciprofloxacin using 0.1N HCL

The calibration curve was plotted between the concentration and absorbance. The calibration curve of 5-30 µg / ml was carried out. The slope and intercept of the calibration curve were 0.013 and 0.010 respectively. The correlation coefficient 'r^2' values were calculated as 0.998.

Table : Calibration curve of Ciprofloxacin in 0.1NHCL

S. No.	Concentration(µg/ml)	Absorbance at 276.0nm
1	0	0
2	5	0.088
3	10	0.154
4	15	0.224
5	20	0.286
6	25	0.352
7	30	0.428

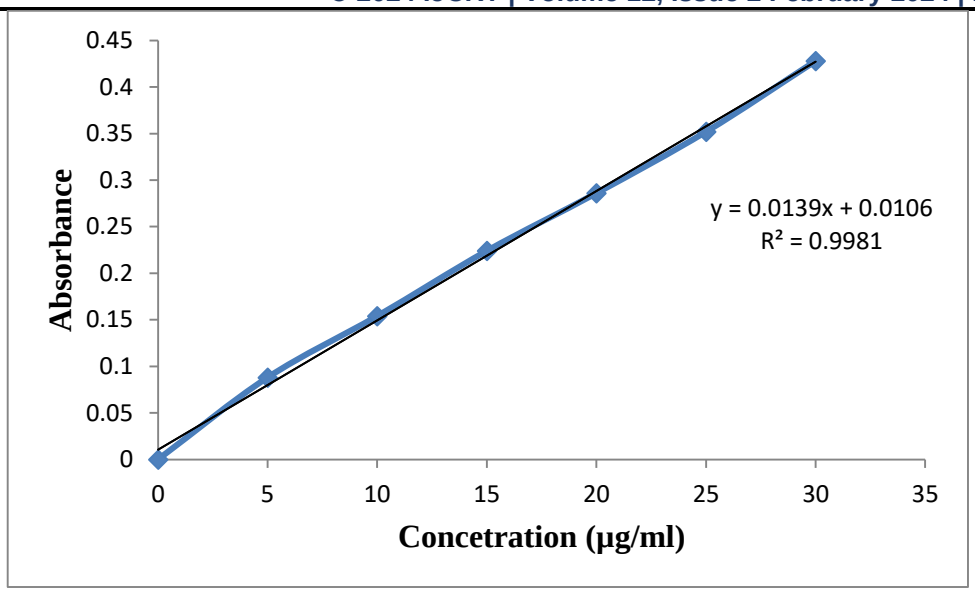

Fig 2: Calibration Curve of Ciprofloxacin in 0.1N HCL

Partition Coefficient

Table 7: Partition Co-efficient

Sr.No.	Solvents	Absorbance
1	Water	0.378
2	N-hexane	0.363

Partition coefficient = concentration of n-hexane/concentration of water

Concentration of n-hexane: Y-0.013X+0.010

0.363=0.013X+0.010

X=0.363-0.010/0.013=27.15

Concentration of water: Y=0.013+0.010

0.0378=0.013X+0.010

X= 0.378-0.010/0.013 = 28.30

Partition coefficient$_{/w}$ = 27.15/28.30=0.959

FT-IR Determination

The IR spectrum of Ciprofloxacin substance was authenticated using IR spectroscopy. The presence of characteristic peaks associated with specific structural characteristics of the drug molecule was noted and the graph was shown in fig. 7.3.

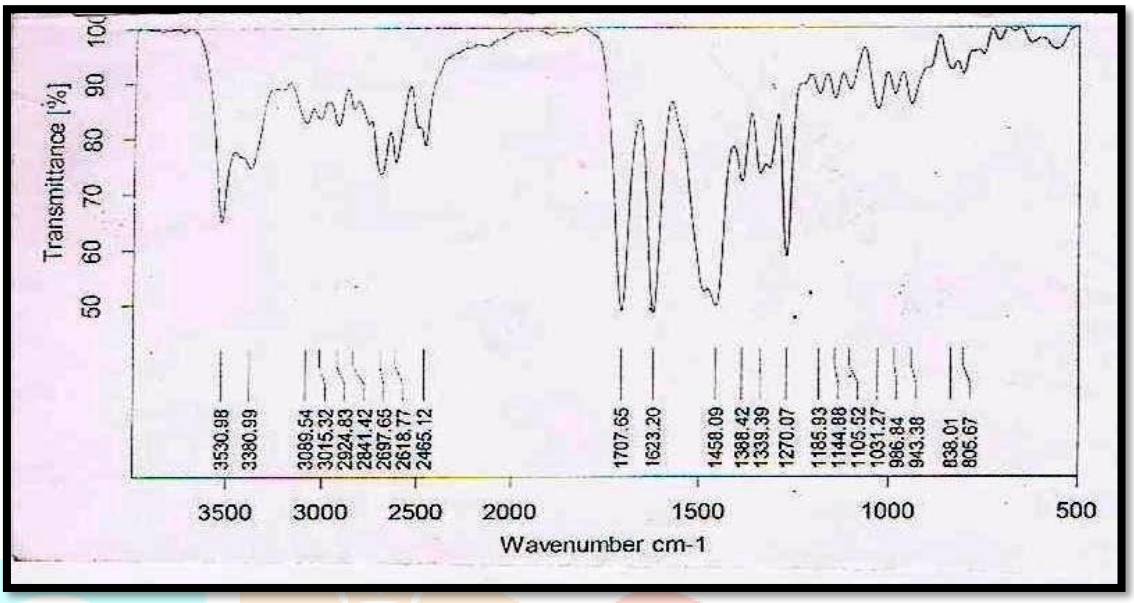

Fig 3: FT-IR of Pure Drug (Ciprofloxacin)

Table 8: Peaks Observed in FTIR Spectra

Peak (cm^{-1})	Groups	Observed Peak Value(cm^{-1})
3500-3540	Hydroxyl group	3530
3000-2950	Aromatic cyclic enes	3015
1750-1700	CO group of acid	1707
1650-1600	Quinolines	1623
1450-1400	Carbonyl group	1450
1300-1250	Hydroxyl group	1339
1050-1000	Fluorine group	1001

Drug Exciepients Interaction Study

The FT-IR graphs of Drug, Guar Gum and Ethyl cellulose.

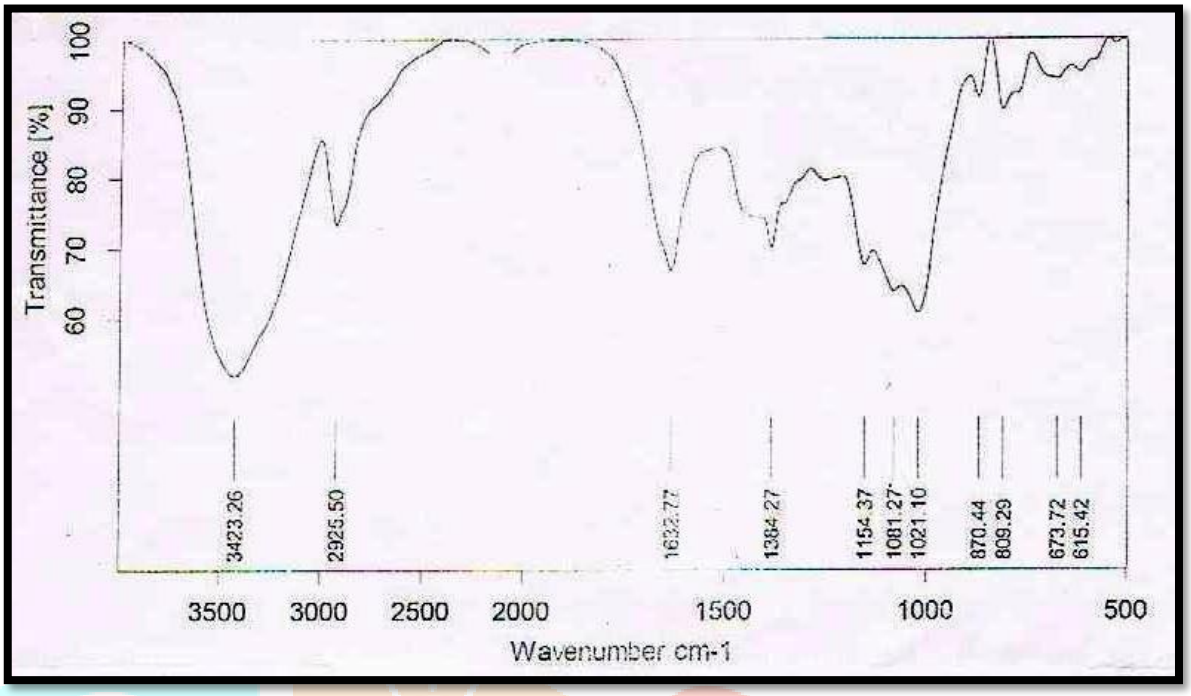

Fig 4: FT-IR of Guar Gum

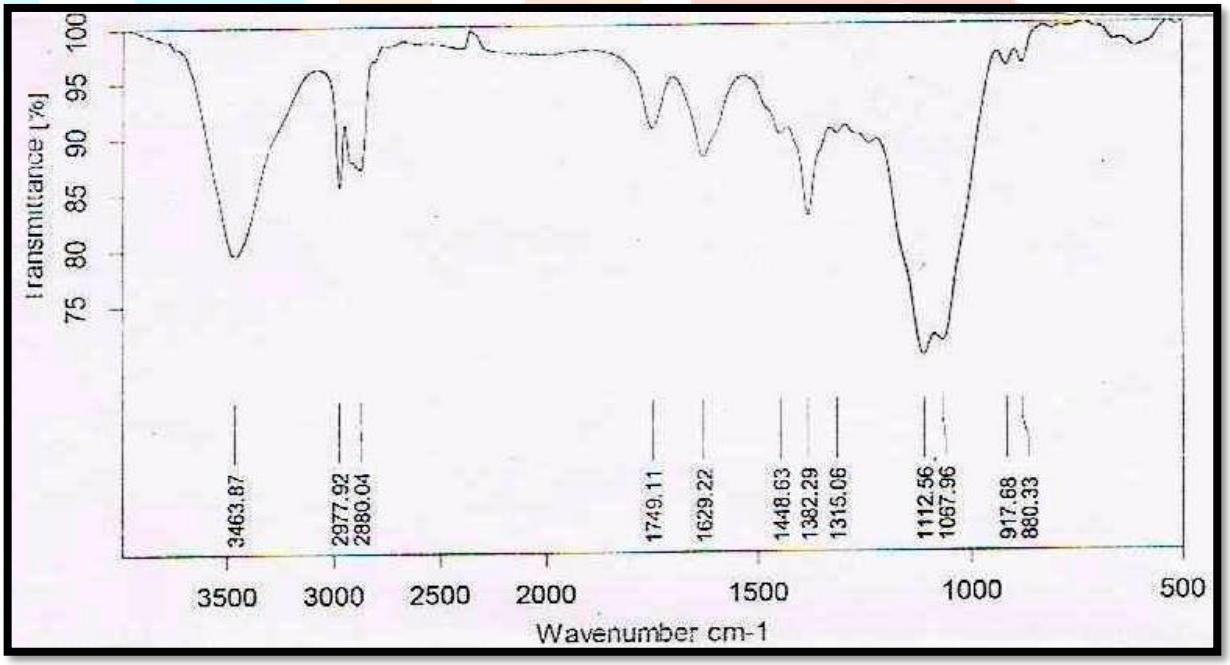

Fig 5: FT-IR of Ethyl Cellulose

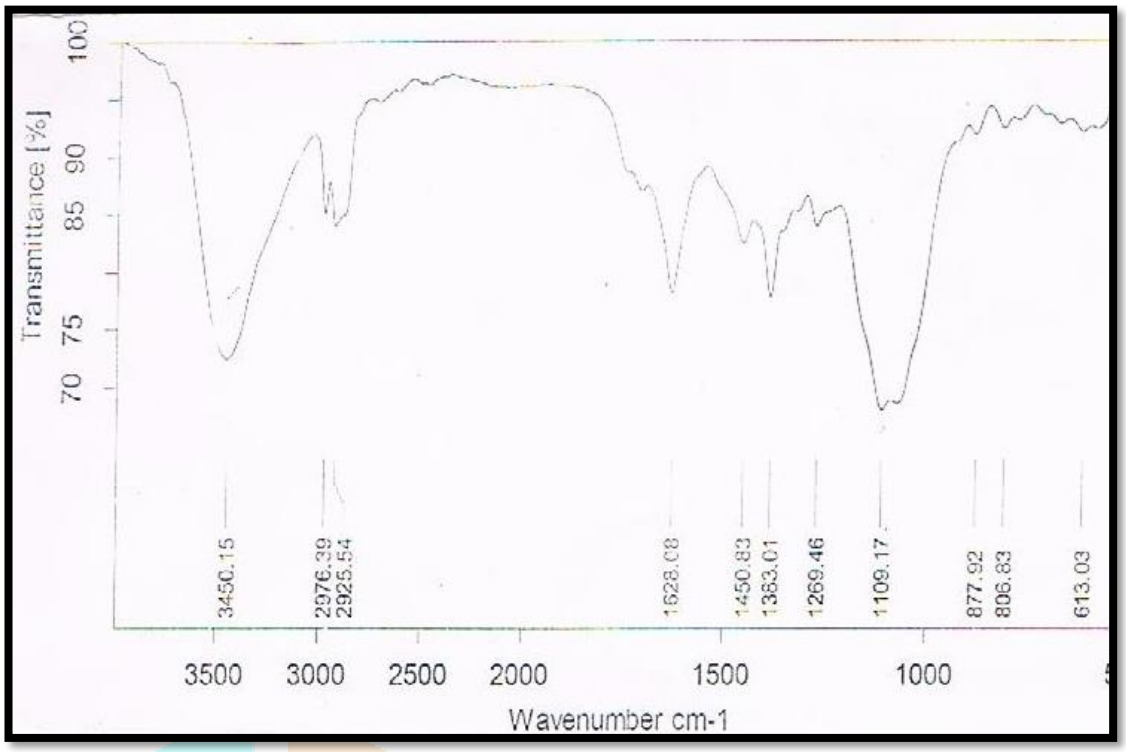

Fig 6: FT-IR of Ciprofloxacin + Guar Gum + Ethyl Cellulose

Ciprofloxacin and the formulations of each polymer were subjected to FT-IR spectroscopic analysis, to ascertain whether there is any interaction between the drugs and the polymers used. The FT-IR spectra obtained is given in Fig. 7.4, 7.5 and 7.6. The characteristic peaks of the pure drug were compared with peaks obtained from their respective formulations respectively. From the data obtained it was observed that characteristic peaks appears with identical or with minor differences, at frequencies 1339 cm^{-1} (C-N stretch), 1707 cm^{-1} (C=O stretch), 1623 cm^{-1} (COOH stretch), 3530 (N-H stretch), 1001 cm^{-1} (C-F stretch) for ciprofloxacin and polymers, from the peaks it was evident that there was no chemical interaction between the drug and polymers.

Evaluation

The present study was taken to formulate and evaluate sustained release microspheres of Ciprofloxacin by using natural and synthetic polymers having two different techniques.

Characteristics of Microspheres Using Synthetic Polymer

The microspheres were white, free-flowing and spherical. The percentage of yield value of synthetic polymer between 91.69±0.052% to 94.28±0.045% and natural polymer between 94.5±1.5% to 95.43±4.7%. The quantitative characteristics of the microspheres are shown in Table 7.8. The drug content of synthetic polymer was better the natural polymers. The drug content of synthetic polymer was between 93.83±1.76 to 98.92±1.90 and the drug content of natural polymer was between 83.67±3.4 to at 87.38±2.6. It was also seen that mean particle size higher then natural polymer. The particle size of synthetic polymer was range between 664±0.016 to 676 ±0.007 and natural polymer was range between 463±2.6 to 608±2.0. The value of entrapment efficiency was found to be in the range of 89.80% to 98.20 % for synthetic formulation and

78.60 to 90.90 % for natural formulation (Table No. 7.8). The percentage efficiency increases with the increase in polymer concentration. The drug entrapment efficiency of ethyl cellulose microspheres was found to be more then Guar gum microspheres.

Table : Some of the Characteristics of the Microspheres (±SD, n = 3)

Batch Code	Yield (%)	Drug Content (%)	Mean Particle size (µm)	Encapsulation Efficiency %
SF1	94.28±0.045	94.42±1.41	644 ±0.016	89.80 ±0.025
SF2	92.46±0.038	93.83±1.76	663±0.012	92.70 ±0.038
SF3	91.69±0.052	98.92±1.90	676 ±0.007	98.20 ±0.059
NF1	95. 43±4.7	83.67±3.4	463±2.6	78.6±1.3
NF2	93.24±2.6	87.38±2.6	521±4.4	86.2±2.0
NF3	94.5±1.5	85.94±3.2	608±2.0	90.9±1.8

The shape and surface morphology of the guar gum and ethyl cellulose microspheres can be described by SEM (Fig.7.8&7.7) the microspheres are spherical and uniform in shape. The SEM micrographs of microspheres show a rough and folded surface morphology.

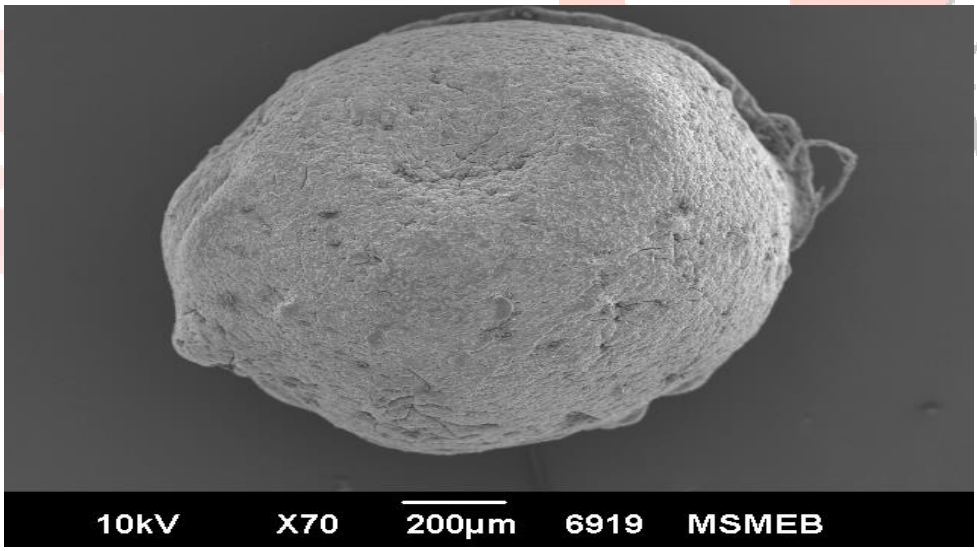

Fig. 7: SEM Image of Ciprofloxacin Microcapsule Using EC

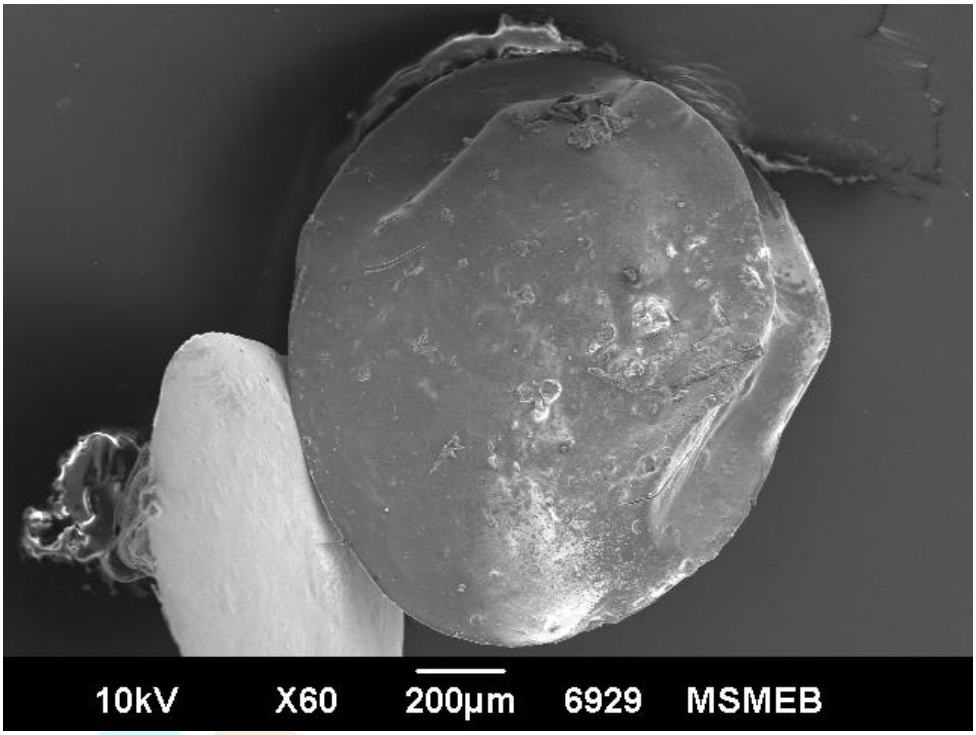

Fig.8: SEM Image of Ciprofloxacin Microcapsule Using Guar Gum

Above all the formulation, we had selected formulation No SF3 and NF3 for further release study. It was observed from that the steady state release was achieved after initial lag time and it was directly proportional to the polymer concentrations in both the cases. The first phase might be for negligible dissociation of microspheres in simulated gastric fluid during first two hours and the drug release mainly based on drug diffusion through pores and cracks or may be due to the swelling of polymer. The second phase exhibited a burst- like release pattern, which was accomplished by the polymer disintegration due to enzymatic degradation of polymer. Both the polymers are highly branched and the highly branched molecular structure of these polymers resist enzymatic breakdown in digestive tract. The Ethyl Cellulose showed high rate and extent of drug release. The cumulative drug release from SF3 with 97.913 % in 24 hrs (Table No. 7.10). The Guar gum is having release retarding property as compare to Ethyl cellulose. The drug release from NF3with maximum 96.241 % in 24 hrs respectively (Table No. 7.11). This indicates that the synthetic Polymer give better release action as compare to natural polymer.

***In-Vitro* Release Studies**

Table 10: *In-Vitro* Release Profile of Ciprofloxacin Microsphere using Ethyl Cellulose

1. **F1- Formulation**

Time (hr.)	S.Q. T.	Log T.	Abs.	Conc. (Mcg.)	Amt.in 5 ml	Amt.in 900 ml	Correction factor	C.R.	Log %C. R.	D. remaining	Log % Drug Release
0	0	0	0	0	0	0	0	0	0	100	2
1	1	0	0.35	19.166	0.095	17.249	-	17.249	1.236	82.751	1.917
2	1.414	0.301	0.60	33.055	0.165	29.74	0.095	29.835	1.474	70.165	1.846
4	2	0.602	0.75	41.388	0.206	32.08	0.26	32.34	1.509	67.66	1.83
6	2.449	0.778	0.89	49.166	0.245	44.1	0.466	44.566	1.649	55.434	1.743
8	2.828	0.903	1.01	55.833	0.279	50.22	0.711	50.931	1.706	49.069	1.69
10	3.162	1.00	1.20	66.388	0.331	59.58	0.99	60.57	1.782	39.43	1.595
12	3.464	1.079	1.55	85.833	0.429	77.22	1.321	78.541	1.895	21.454	1.331
16	4	1.204	1.60	88.611	0.443	79.74	1.75	81.49	1.911	18.51	1.267
18	4.242	1.255	1.65	91.388	0.456	82.08	2.193	84.273	1.925	15.727	1.196
20	4.472	1.301	1.72	95.277	0.476	85.68	2.649	88.329	1.946	11.671	1.067
24	4.898	1.380	1.80	99.722	0.498	89.64	3.125	92.765	1.967	7.235	0.859

2. **F2- Formulation**

Time (hr.)	Abs.	Conc. (Mcg.)	Amt. in 5 ml	Amt.in 900 ml	Correction factor	C.R.	% C.R.	Log %C. R.	D. remaining	Log % Drug Release
0	0	0	0	0	0	0	0	0	100	2
1	0.40	21.944	0.109	19.62	_	19.62	19.62	1.292	80.38	1.905
2	0.64	35.277	0.176	31.68	0.109	31.789	31.789	1.502	68.211	1.833
4	0.80	44.166	0.220	39.6	0.285	39.885	39.885	1.600	60.115	1.778
6	0.96	53.055	0.265	47.7	0.505	48.205	48.205	1.683	51.795	1.714
8	1.19	65.833	0.329	59.22	0.77	59.99	59.99	1.778	40.01	1.602
10	1.30	71.944	0.359	64.62	1.099	65.719	65.719	1.817	34.281	1.535
12	1.63	90.277	0.451	81.18	1.458	82.638	82.638	1.917	17.362	1.239

16	1.70	94.166	0.470	84.6	1.909	86.509	86.509	1.937	13.491	1.13
18	1.74	96.388	0.481	86.58	2.379	88.959	88.959	1.949	11.041	1.065
20	1.81	100.27	0.501	90.18	2.86	93.04	93.04	1.968	6.96	0.842
24	1.85	102.5	0.512	92.16	3.361	95.521	95.521	1.980	4.479	0.65

3. F3-Formualation

Time (hr.)	Abs.	Conc. (Mcg.)	Amt. in 5 ml	Amt.in 900 ml	Correction factor	C.R.	% C.R.	Log %C.R.	D. remaining	Log % Drug Release
0	0	0	0	0	0	0	0	0	100	2
1	0.44	24.166	0.120	21.6	_	21.6	21.6	1.334	78.4	1.894
2	0.67	36.944	0.184	33.12	0.120	33.24	33.24	1.521	66.76	1.824
4	0.90	49.722	0.248	44.64	0.304	44.944	44.944	1.652	55.056	1.74
6	0.99	66.388	0.273	49.14	0.552	49.692	49.692	1.696	50.308	1.701
8	1.20	76.944	0.331	59.58	0.825	60.405	60.405	1.781	39.591	1.597
10	1.39	80.277	0.384	69.12	1.156	70.276	70.276	1.846	29.724	1.473
12	1.45	88.611	0.401	72.18	1.54	73.72	73.72	1.86	26.28	1.419
16	1.60	94.166	0.443	79.74	1.941	81.681	81.681	1.912	18.319	1.262
18	1.70	100.27	0.470	84.6	2.411	87.011	87.011	1.939	12.989	1.113
20	1.81	111.38	0.501	90.18	2.912	93.092	93.092	1.968	6.908	0.839
24	1.90	105.27	0.525	94.5	3.413	97.913	97.913	1.990	2.087	0.319

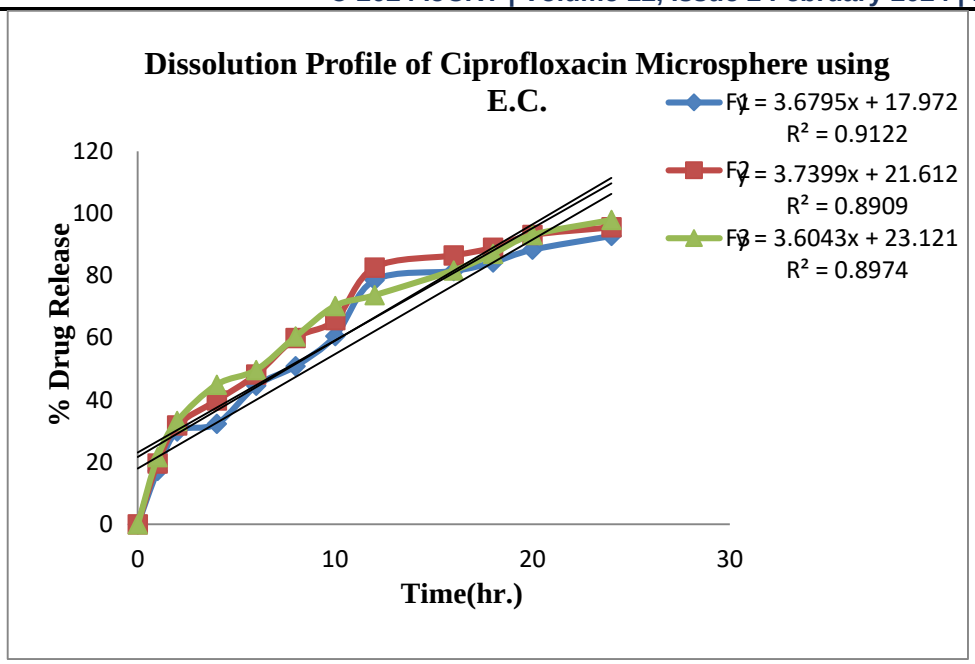

Fig. 9: Dissolution Profile of Ciprofloxacin Microsphere using Ethyl Cellulose

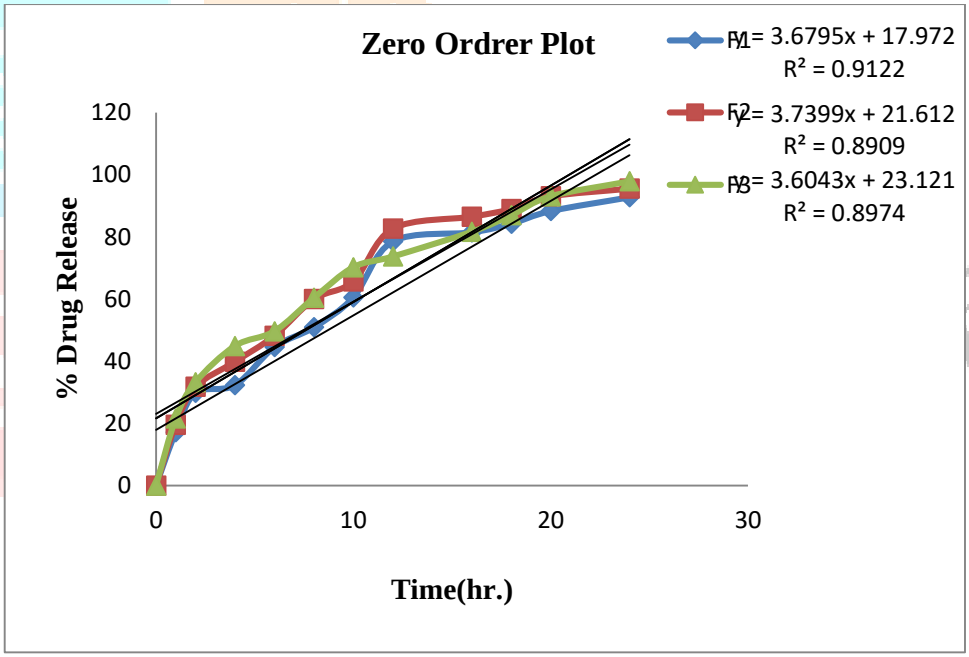

Fig. 10: Zero Order Kinetic study of Ciprofloxacin Microsphere using Ethyl Cellulose

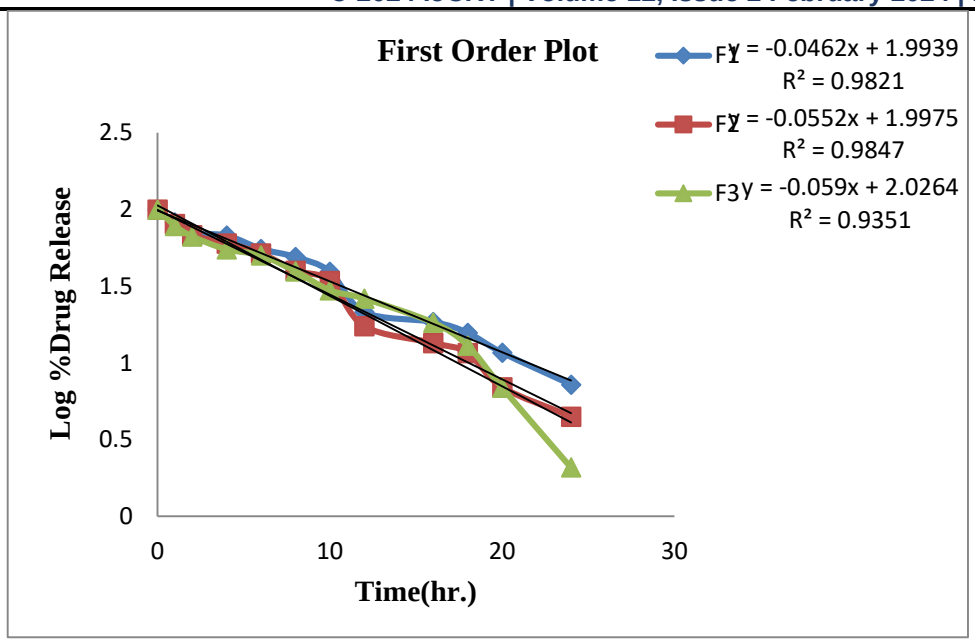

Fig. 11: First Order Kinetic study of Ciprofloxacin Microsphere using Ethyl Cellulose

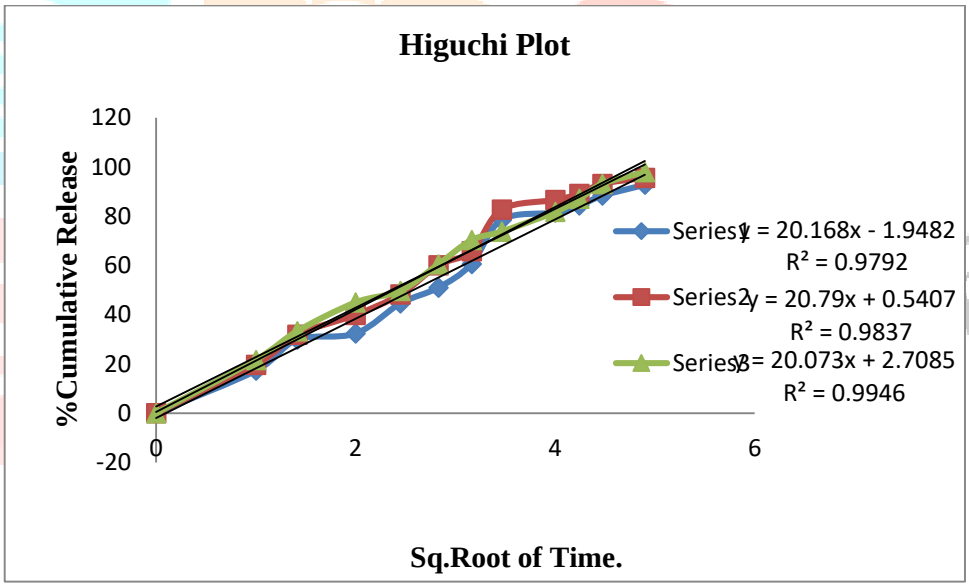

Fig 12: Higuchi Equation of Ciprofloxacin Microsphere using Ethyl Cellulose

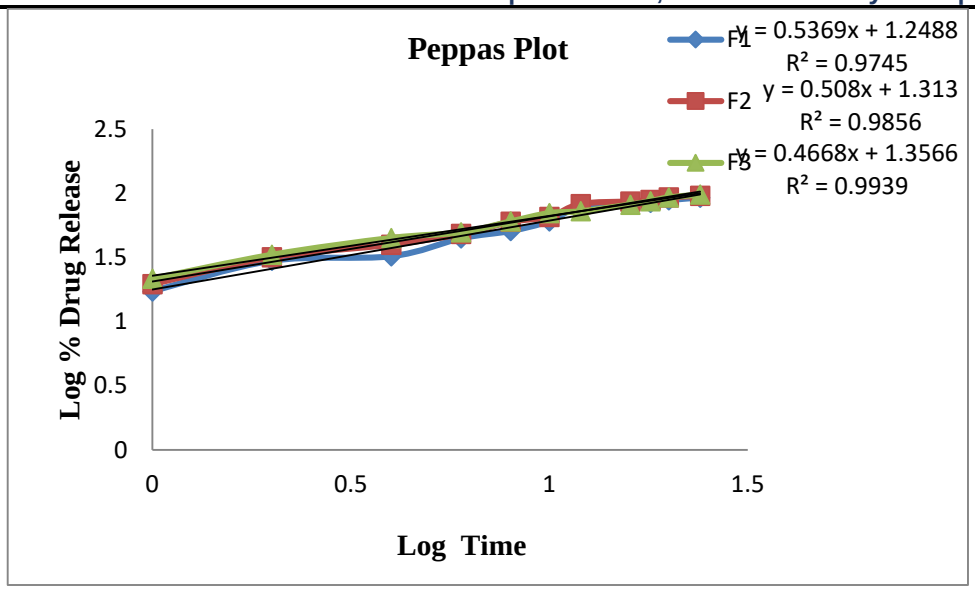

Fig. 13: Peppas Equation Ciprofloxacin Microsphere using Ethyl Cellulose

Table 11: *In-Vitro* Release Profile of Ciprofloxacin Microsphere using Guar Gum

1. F1-Formualation

Time (hr.)	Abs.	Conc. (Mcg.)	Amt. in 5 ml	Amt.in 900 ml	Correction Factor	C.R.	% C.R.	Log %C.R.	D. Remaining	Log % Drug Release
0	0	0	0	0	0	0	0	0	100	2
1	0.50	33.055	0.165	29.7	-	29.7	29.7	1.472	70.3	1.846
2	0.69	38.055	0.190	34.2	0.165	34.365	34.365	1.536	65.635	1.817
4	0.75	41.388	0.206	37.08	0.355	37.435	37.435	1.573	62565	1.796
6	0.83	45.833	0.229	41.22	0.561	41.781	41.781	1.620	58.219	1.765
8	0.98	54.166	0.270	48.6	0.79	49.39	49.39	1.693	50.61	1.704
10	1.15	63.611	0.318	57.24	1.06	58.3	58.3	1.765	41.7	1.620
12	1.30	71.944	0.359	64.62	1.378	65.998	65.998	1.819	34.002	1.531
16	1.41	78.055	0.390	70.2	1.737	71.937	71.937	1.856	28.063	1.448
18	1.50	83.055	0.415	74.7	2.127	76.827	76.827	1.885	23.173	1.364
20	1.66	91.944	0.459	82.62	2.542	85.162	85.162	1.930	14.838	1.171
24	1.87	103.61	0.518	93.24	3.001	96.241	96.241	1.983	3.759	0.575

2. F2-Formualation

Time (hr.)	Abs.	Conc. (Mcg.)	Amt. in 5 ml	Amt.in 900ml	Correction factor	C.R.	%C.R.	Log %C.R.	D. remaining	Log % Drug Release
0	0	0	0	0	0	0	0	0	100	2
1	0.46	25.277	0.126	22.68	-	22.68	22.68	1.355	77.32	1.888
2	0.62	34.166	0.170	30.6	0.126	30.726	30.726	1.487	69.274	1.840
4	0.84	46.388	0.231	41.58	0.296	41.876	41.876	1.621	58.124	1.764
6	0.96	53.055	0.265	47.7	0.527	48.227	48.227	1.683	51.773	1.714
8	0.99	54.722	0.273	49.14	0.792	49.932	49.932	1.698	50.006	1.699
10	1.10	60.833	0.304	54.72	1.065	55.785	55.785	1.746	44.215	1.645
12	1.21	66.944	0.334	60.12	1.369	61.489	61.489	1.788	38.52	1.585
16	1.32	73.055	0.365	65.7	1.703	67.403	67.403	1.828	32.597	1.513
18	1.42	78.611	0.393	70.74	2.068	72.808	72.808	1.862	27.197	1.434
20	1.49	82.5	0.412	74.16	2.461	76.621	76.621	1.884	23.379	1.368
24	1.58	87.5	0.437	78.66	2.873	81.533	81.533	1.911	18.467	1.266

3. F3-Formualation

Time (hr.)	Abs.	Conc. (Mcg.)	Amt. in 5 ml	Amt.in 900ml	Correction factor	C.R.	%C.R.	Log %C.R.	D. remaining	Log % Drug Release
0	0	0	0	0	0	0	0	0	100	2
1	0.50	27.5	0.135	24.3	-	24.3	24.3	1.38	75.7	1.879
2	0.67	36.944	0.184	33.12	0.135	33.255	33.255	1.521	66.745	1.824
4	0.75	41.388	0.206	37.08	0.319	37.399	37.399	1.572	62.601	1.796
6	0.85	46.944	0.234	42.12	0.525	42.645	42.645	1.629	57.355	1.758
8	1.01	55.833	0.279	50.22	0.759	50.979	50.979	1.707	49.021	1.690
10	1.10	60.883	0.304	54.72	1.038	55.758	55.758	1.746	44.242	1.645
12	1.20	66.388	0.331	59.58	1.342	60.922	60.922	1.784	39.078	1.591
16	1.27	70.277	0.351	63.18	1.673	64.853	64.853	1.811	35.147	1.545
18	1.35	74.722	0.373	67.14	2.029	69.164	69.164	1.839	30.836	1.589
20	1.45	80.277	0.40	72.18	2.397	74.57	74.57	1.872	25.423	1.405

			1			7	7			
24	1.55	85.833	0.429	77.22	2.798	80.018	80.018	1.903	19.982	1.300

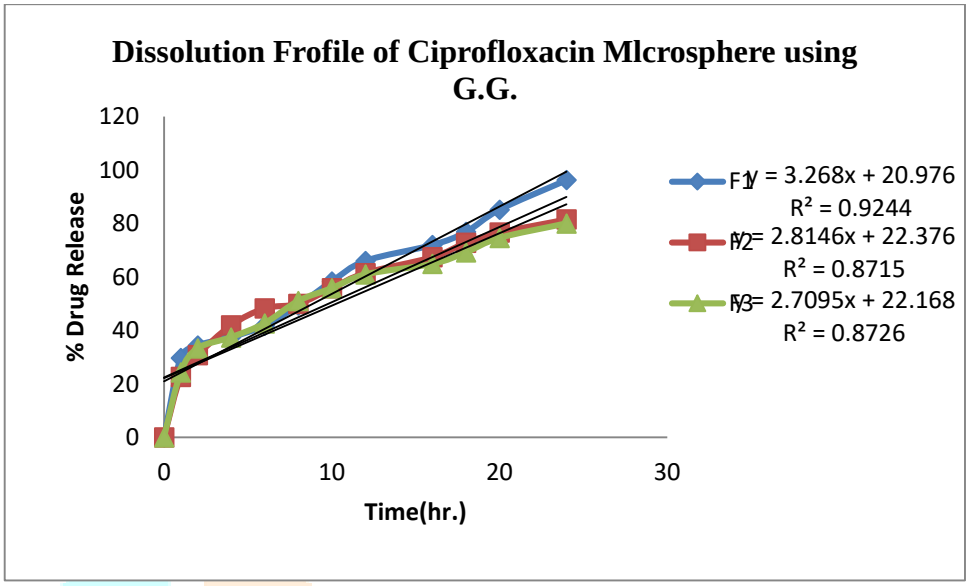

Fig. 14: Dissolution Profile of Ciprofloxacin Microsphere using Guar Gum

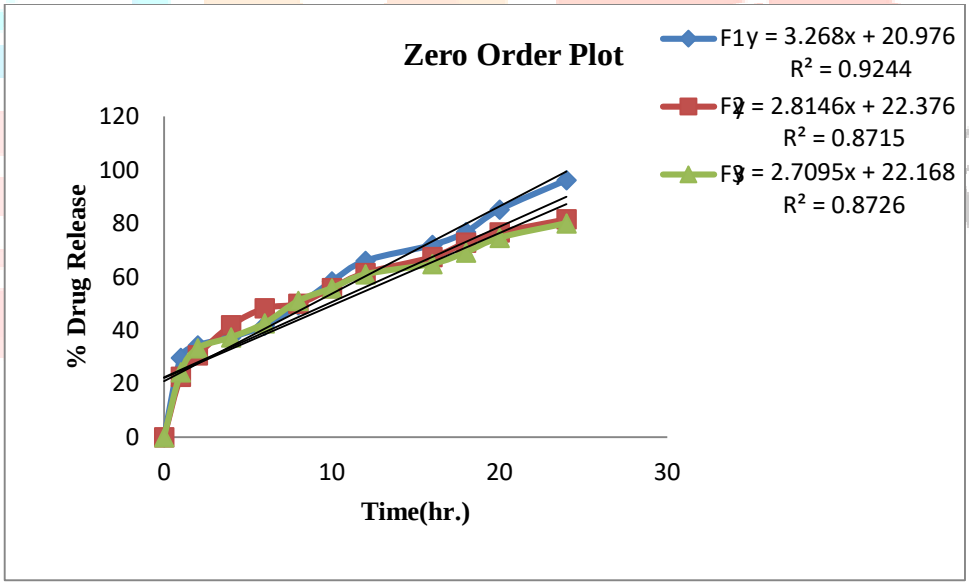

Fig. 15: Zero Order Kinetic study of Ciprofloxacin Microsphere using Guar Gum

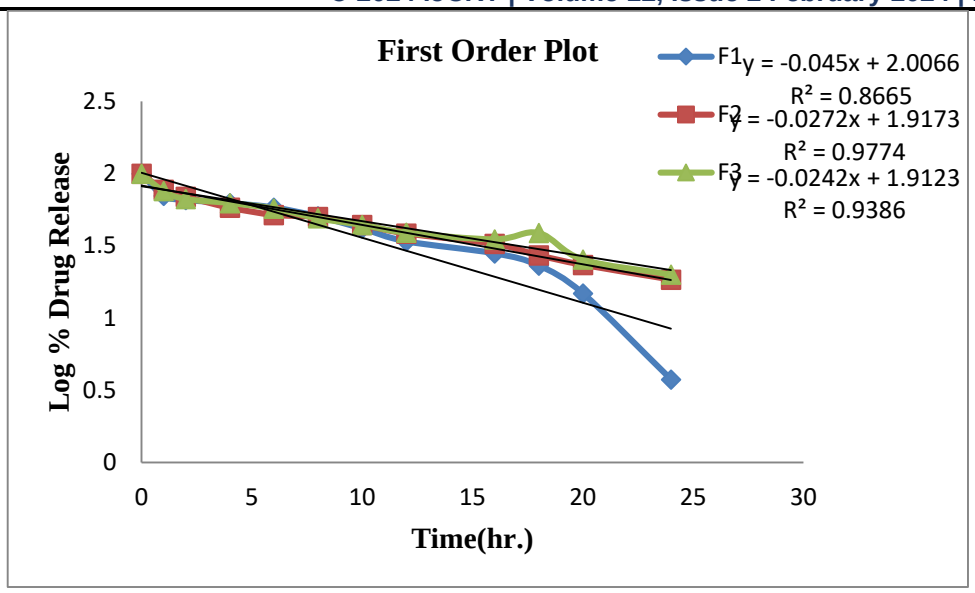

Fig. 16: First Order Kinetic study of Ciprofloxacin Microsphere using Guar Gum

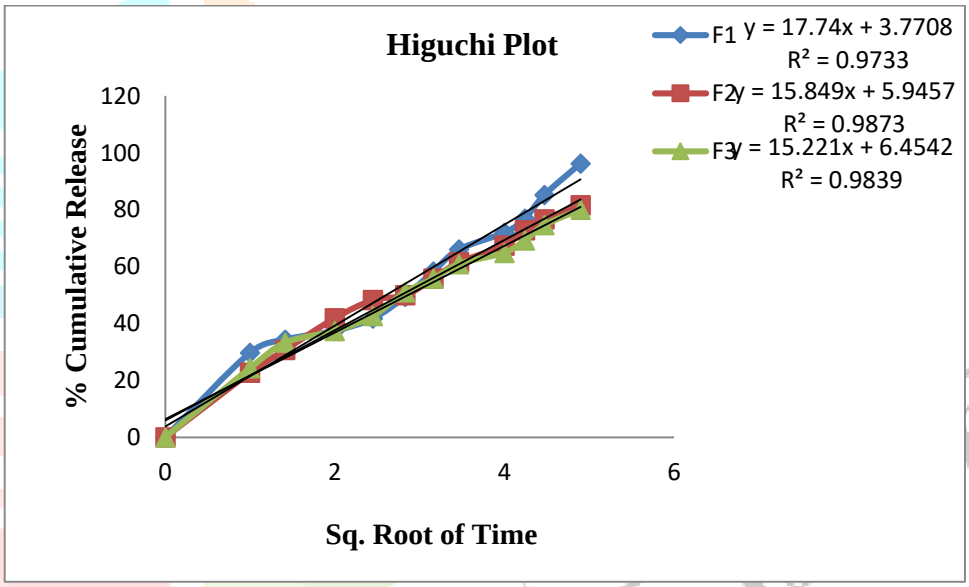

Fig. 17: Higuchi Equation of Ciprofloxacin Microsphere using Guar Gum

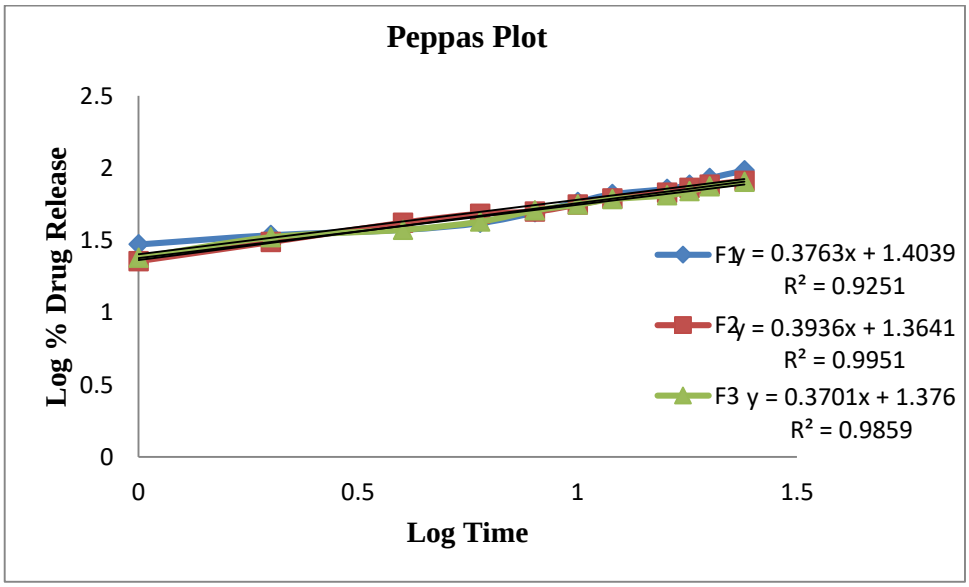

Fig. 17: Peppas Equation of Ciprofloxacin Microsphere using Guar Gum

Table 12: Correlation Coefficient (R^2) and Constant (K) of different Kinetic Models for Ciprofloxacin Microspheres

	E.C. Microsphere					
Zero Order	**F1R²**	**F2 R²**	**F3R²**	**F1K₀**	**F2K₀**	**F2K₀**
	0.912	3.73	3.60	3.679	3.739	3.604
First Order	**F1R²**	**F2 R²**	**F3R²**	**F1K₁**	**F2K₁**	**F3K₁**
	0.982	0.984	0.935	-0.046	-0.055	-0.059
Higuchi Equation	**F1R²**	**F2 R²**	**F3R²**	**F1K$_H$**	**F2K$_H$**	**F3K$_H$**
	0.979	0.983	0.994	20.16	20.79	20.07
Peppas Equation	**F1R²**	**F2 R²**	**F3R²**	**F1K$_P$**	**F2K$_P$**	**F3K$_P$**
	0.974	0.985	0.993	0.536	0.508	0.466

Table 13: Correlation Coefficient (R^2) and Constant (K) of different Kinetic Models for Ciprofloxacin Microspheres

	G.G. Microsphere					
Zero Order	**F1R²**	**F2 R²**	**F3R²**	**F1K₀**	**F2K₀**	**F2K₀**
	0.924	0.871	0.872	3.260	2.814	2.709
First Order	**F1R²**	**F2 R²**	**F3R²**	**F1K₁**	**F2K₁**	**F3K₁**
	0.866	0.977	0.938	-0.045	-0.027	0.024
Higuchi Equation	**F1R²**	**F2 R²**	**F3R²**	**F1K$_H$**	**F2K$_H$**	**F3K$_H$**
	0.973	0.987	0.983	17.74	15.84	15.22
Peppas Equation	**F1R²**	**F2 R²**	**F3R²**	**F1K$_P$**	**F2K$_P$**	**F3K$_P$**
	0.925	0.995	0.985	0.376	0.393	0.370

REFERENCES:

- Ali J. Khar, R.K. Ahuja "Textbook of Dosage Form Design" Birla Publications Pvt. Ltd. Delhi 2007; 17:3,16-17
- Aulton ME. "Hand Book of Pharmaceutics" ELBS with Churchill Livingstone, Hong Kong 2001; 291-295.
- A. Pandey, B. Rathi, AK. Dwivedi. "Pharmaceutical Preformulation Studies with Special Emphasis on Excipients Compatibility" Available Online Through Review Article. International Journal of Pharmacy & Technology Page no.1029-1040
- Ballard BE. "An overview of prolonged action drug dosage forms" In sustained and controlled release drug delivery systems. Robinson JR. New York 1978.
- Banker GS, Rhodes CT. "Modern pharmaceutics" Marcel Dekker, New York 2002;1(4): 503-519, 678-721
- Barar FSK. Essentials of Pharmacotherapeutics. S Chand and company Ltd. New delhi 2007; 4, 215, 246
- Brahmankar DM, Jaiswal SB."Biopharmaceutics and Pharmacokinetics" Vallabh Prakashan 1995; 1: 292-293, 347- 352
- Balaji Venkataramanappa Kadri "Mechanism Of Drug Release From Matrix Tablets, Involving Moving Boundaries" Master of Science, 2001,Department of pharmaceuticals sciences University of Toronto, international journal of Pharma science 2001 Page no.5, 6, 7
- Clark's Analysis of Drug and, London: Pharmaceutical Press, Electronic version Poison 2005 3 158, 458, 987
- Dr k. L. Senthilkumar and R. P. Ehizilmuthu. "Formulation Development And Evaluation of Metformin Hydrochloride SR Tablets" International Journal of Pharma and Bio Sciences, vol2, 2011 Page no. 79, 80
- Dr. Umesh D. Shivhare, Nandkishor D. Adhao, Dr. Kishore. P. Bhusari, Dr. Vijay B. Mathur, Mr Digvijay U. Ambulkar, "Formulation Development Evaluation And Validation Of Sustained Release Tablets Of Aceclofenac" 2009 J. Excipients and Food Chem. 2010 Page no. 75, 76
- Dr.A.Lakshmi Prasad, Senior Manager (Analytical Research) Senior Manager (Analytical Research). Sun Pharma Advanced Research Co.Ltd,. Drug - Excipient interactions Excipient interactions. "International Convention Center International Convention Center" Page no.18, 19.
- Dangi Amish. A, Manish Kumar Rai, Shukla Tapan M, "Formulation and Optimization of Extended Release Metformin Hydrochloride Tablet: Effects of Polymers and Additives on Drug Release Mechanism"Asian Journal of Biochemical and Pharmaceutical Research, Vol-I. 2011 Page no 481-486.