Research Article

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Formulation and Evaluation of Controlled Release Matrix Tablets of Ciprofloxacin by Using Natural Polymer

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Abstract:

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its case of administration and the belief that oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Keywords:

Cefuroxime axetil, Oral Drug Delivery, Controlled Release Matrix Tablets, Ciprofloxacin, Natural Polymers.

1. INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its case of administration and the belief that oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form[1].

1.1 Rationale of sustained and controlled drug delivery:

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a dosing property of a rate controlled dosage form and less or not at all the property of the drug molecules properties, inherent kinetics. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetic and pharmacodynamics of the drugs[2].

1.2 Sustained and controlled release drug delivery system:

Over the past 30 years, as the expense and complications involved in marketing now drug entities have increase, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered or applied by conventional method in the form of tablets, capsules, injections, ointments etc. usually conventional dosage form produces wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of controlled delivery system. The goal in designing sustained or controlled delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one

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or more drugs continuously in predetermined pattern for a fixed period of time, either systematically or to a specified target organ, controlled release dosage forms provide a better control of pharma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

1.3 Terminology[3]:

Modified release delivery systems may be divided conveniently into four categories.

A. Delayed Release
B. Sustained Release
C. Controlled Release
D. Extended Release
E. Site specific targeting drug delivery
F. Reception targeting drug delivery

A. Delayed Release: These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release system include repeated action tablets and capsules and enteric-coated tablets where timed to release is achieved by a barrier coating.

B. Sustained Release: These systems include any drug delivery system that achieves slow, release of drug over an extended period of time.

C. Controlled Release: These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

D. Extended Release: Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduces the dosage frequency by two folds.

E. Site specific targeting drug delivery: These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

F. Reception targeting drug delivery: These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for drug within an organ or tissue, site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

1.4 Types of sustained and controlled release system[5,7]:

Total 5 types of oral controlled release systems are available, classified based on the release mechanism:

A. Dissolution controlled release system
B. Diffusional controlled release system
C. Bioerodible and combination diffusion and dissolution systems.
D. Osmotically controlled release systems
E. Ion exchange systems.

A. Dissolution controlled release system: A drug with a slow dissolution rate will sustain release rate of the drug from the dosage form. Here the rate –limiting step is dissolution. This being true, decreasing their rate of dissolution could make sustained release preparation of drugs. These approaches are achieved by preparing appropriate salts or derivatives, coating the drug with a slow dissolving material or incorporating it into a tablet with a slowly dissolving carrier.

B. Diffusional systems: It this system release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer.

C. Reservoir devices:

A core of drug, the reservoir, surrounded by a polymeric membrane, characterizes reservoir devices. The nature of the membrane determines the rate of release of drug from the system.

a. Matrix devices: Matrix devices consist of drug dispersed homogenously, throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system, rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

b. Bioerodible and combination diffusion and dissolution system:

Bioerodible devices constitute a group of systems for which release characteristics are complex. The mechanism of release from simple erodible slabs, cylinders and spheres can be described by following mathematical model

$$Mt/M=1-(1-Kot/Coa)n$$

Where
Mt= Mass of drug release at time t
M = Mass release at infinite time.
a = Radius of a sphere or cylinder or the half height of a slab.
n = 3 for a sphere, 2 for a cylinder and 1 for slab.

This system is the combination of both diffu-

sion and dissolution of matrix material and the drug. Drug not only can diffuse out of the dosage from but the matrix itself undergoes a dissolution process.

c. Osmotically controlled system:

In these systems, osmotic pressure provides the driving force to generate controlled release of drug. In this system a tablet containing a core of drug surrounded by a semipermiable membrane, which is permeable to water, but not to drug. When this device is exposed to water or any body fluid, water will flow into the tablet owing to the osmotic pressure difference.

d. Ion exchange systems:

This system generally use resins composed of water insoluble cross linked polymers. These polymers contain salt forming functional groups in repeating positions on the polymer chain. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion exchange groups

$$\mathbf{Resin^{+} - drug^{-} + x^{-} \rightarrow Resin^{+} - x^{-} + drug^{-}}$$

Conversely

$$\mathbf{Resin^{-} - drug^{-} + Y^{+} = Resin^{-} - Y^{+} + drug^{+}}$$

Where x^{-} and y^{+} are ions in the GI tract.

The free drug then diffuses out of the resin. The drug resin complex is prepared by repeated exposure of the resin to the drug in a chromatography column, or by prolonged contact in solution.

1.5 Drug properties adversely influencing controlled – release dosage form[6]:

Physical – Chemical Properties:

a. Dose size: If an oral product has a dose size greater than 0.5gm; it is a poor candidate for sustained release systems, since addition of the sustaining mechanism will, in most cases, generates a substantial volume product that will be unacceptably large.

b. Aqueous Solubility: Extremes in aqueous solubility are undesirable in the preparation of a sustained release product. For drugs with low water solubility, they will be difficult to incorporate into a sustained release product. For drugs with low water solubility, they will be difficult to incorporate into a sustained release mechanism. The lower limit on solubility for such product has been reported to be 0.1 mg/ml drugs with great water solubility are equally difficult to incorporate into a sustained release system. pH – dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

c. Partition coefficient: Drugs that are very lipid soluble or very water soluble, i.e. extremes in partition coefficient, will demonstrate either low flux into the tissues or rapid flux followed by accumulation in the tissues. Both cases are undesirable for a sustained release system.

d. Drug stability: Since most oral sustained release systems by necessity, are designed to release their contents over much of the length of the GI tract, drugs, which are unstable in the environment of the intestine, might be difficult to formulate into prolonged release systems. Interestingly placement of a labile drug in a sustained release dosage form often improves the bioavailability picture.

Biological Properties:

a. Absorption: Drugs that are slowly absorbed or absorbed with a variable absorption rate are poor candidates for a sustained release system. For oral dosage forms, the lower limit on the absorption rate constant is in the range of 0.25 h -1 (assuming a GI transit time of 10-12h).

b. Distribution: Drugs with high apparent volumes of distribution, which in turn influences the rate of elimination for the drug, are poor candidates.

c. Metabolism: Sustained release systems for drugs which are extensively metabolized is possible as long a the rate of metabolism is not too great nor the metabolism variable with GI transit or other routes.

d. Duration of action: The biological half-life and hence the duration of action of a drug obviously plays a major role in considering a drug for sustained release systems. Drugs with short half-lives and high doses impose a constraint because of the dose size needed and those with long half-lives are inherently sustained.

e. Therapeutic: Drugs with a narrow therapeutic range require precise control over the blood levels of drug, placing a constraint on sustained release dosage forms.

1.6 Drawbacks Associated with Conventional Dosage Forms:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication

or over medication.;

3. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.7 Advantages of Controlled Release Drug Delivery Systems:

Therapeutic advantage: Reduction in drug plasma level fluctuation; maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

Reduction in adverse side effects and improvement in tolerability: Drug plasma levels are maintained with in a narrow window with no sharp peaks and with AUC of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release dosage forms.

Patient comfort and compliance: Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

Reduction in healthcare cost: The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product. With reduction in side effects, the overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increase as we approach the maximum safe concentration.

Avoid night time dosing: It is also good for patients to avoid the dosing at night time.

1.8 Matrix Tablets:[8,9,10]:

These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials..

Classification Of Matrix Tablets

A. On the Basis of Retardant Material Used: Matrix tablets can be divided in to 5 types.

a. Hydrophobic Matrices (Plastic matrices):

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers.

The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

b. Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

c. Hydrophilic Matrices:

The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups.

- Cellulose derivatives: Methylcellulose 400 and 4000 cPs; hydroxyethylcellulose; hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000 cPs; and sodium carboxymethylcellulose.
- Noncellulose natural or semisynthetic polymers: agar-agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan and modified starches.
- Polymers of acrylic acid: Corbopol 934, the most used variety.

d. Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded

by enzymes generated by surrounding living cells or by nonenzymetic process in to olegomers and monomers that can be metabolised or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

e. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, macroporous; microporous and non-porous systems can be identified:

a. Macroporous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

b. Microporous System:

Diffusion in this type of system occurs essentially through pores. For microporous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

c. Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.9 Advantages of Matrix Tablets:

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds

1.10 Disadvantages of the matrix systems:

- The remaining matrix must be removed after the drug has been released.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.11 Polymers used in Matrix Tablets:

1. Hydrogels: Polyhydroxyethyle methylacrylate (PHEMA),Cross-linked polyvinyl alcohol (PVA),Cross-linked polyvinyl pyrrolidone (PVP),Polyethylene oxide (PEO),Polyacrylamide (PA),

2. Soluble Polymers: Polyethylene glycol (PEG),Polyvinyl alcohol (PVA),Polyvinyl pyrrolidone (PVP),Hydroxypropyl methyl cellulose (HPMC)

3. Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters

4. Non-Biodegradable Polymers: Polyethylene vinyl acetate (PVA),Polydimethyl siloxane (PDS),Polyether urethane (PEU),Polyvinyl chloride (PVC),Cellulose acetate (CA),Ethyl cellulose (EC)

5. Mucoadhesive polymers: Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin.

6. Natural gums: Xanthan gum,Guar gum,Karaya gum

1.12 Ciprofloxacin:[11, 12]

Ciprofloxacin is a synthetic chemotherapeutic antibiotic of the fluoroquinolone drug class. It is a second-generation fluoroquinolone antibacterial. It kills bacteria by interfering with the enzymes that cause DNA to rewind after being copied, which stops DNA and protein synthesis.

Mode of action

Ciprofloxacin is a broad-spectrum antibiotic active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV,enzymes necessary to separate bacterial DNA, thereby inhibiting cell division.

This mechanism can also affect mammalian cell replication. In particular, some congeners of this drug family (for example those that contain the C-8 fluorine) display high activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases and are toxic to cultured mammalian cells and in vivo tumor models.

There continues to be debate as to whether or not this DNA damage is to be considered one of the mechanisms of action concerning the severe adverse reactions experienced by some patients following fluoroquinolone therapy.

1.13 Gumkondagogu:[13, 14, 15]

Natural gums are employed in the food, pharmaceutical and cosmetic industries as binders, emul-

sifiers, suspendingagents,disinter gra- tingagents and coating materials in microencapsulation.They are also used as stabilisers, thickeners and binders in paper,-textile,paint,ink and petroleum products.Plantgums have wide application in various industries because of theirlow cost and ready availability and the important properties they confer on products.With the increasing demand for natural gums, it has become necessary to explore newer sources of gums such as gum kondagogu (GKG),a tree gum of India which is yet to be industrially exploited.

GKG is a naturally occurring polysaccharide found in the exudate from the tree Cochlospermum gossypium.Basically, it is a polymer of rhamnose, galacturonicacid, glucuronicacid, β-D-galactopyranose, α-Dglucose, β-D-glucose, galactose, arabinose, mannose and fructose with sugar linkages (1→2) β-D-Galp, (1→6) β-D-Gal p, (1 → 4) β-D-GlcpA, 4-O-Me, α-D-GlcpA and (1 → 2) α-L-Rha. GKG has a high uronic acid content and also contains protein, tannin and soluble fibre. The taste of GKG was slightly acidic.

Gum Kondagogu is a negative charged colloid and a high-molecular weight complex acidic polysaccharide. The general utility of Gum Kondagogu is based on its viscosity. It was successfully evaluated for its suitability in the preparation of hydrophilic matrices, mini-matrices, microcapsules and transdermal patches.

2. MATERIALS AND METHODOLOGY:

2.1 Materials Used:

The following materials used were supplied by the manufacturer are of L.R. or analytical grade

Table No.1: List of Matierials used

S. No	Materials	Grade	Manufacturer
1	Ciprofloxacin	Pure	Doctors Vet Pharma, Nellore
2	Gum kondagogu	Grade I	Girijan Co-operative Corporation Ltd. Hyderabad
3	Carboxy methyl cellulose	LR	Cadila.
4	Starch	LR	Merk
5	Poly vinyl pyrolidine K30	LR	SD Fine chemicals Ltd, Mumbai.
6	Magnesium stearate	LR	SD Fine chemicals Ltd, Mumbai.
7	Iso propyl alcohol	LR	SD Fine chemicals Ltd, Mumbai.

2.2 Equipments Used:

Table No.2: List of Equipements used

S. No.	Equipment	Manufacturer	Model
1	Electronic Single Pan Balance	Sartorius	LA120S
2	Mesh # 12, 14, 16, 18, 40,60,100	Retsec	ASL00
3	Tapped density tester	Electro lab	ETD-1020
4	Analytical Sieve Shaker	Retsec	ASL00
5	Blender	Rimek	410AG
6	Mechanical stirrer	Remi motors , Bombay	RQG-129D
7	Coating pan	Ganscoater	GAC-275
8	Tray drier	MACK	M-552
9	pH meter	Digisum Electronics	707
10	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
11	Stability chambers	Thermo lab	M-722
12	Disintegrating apparatus	Electro lab	ED-2AL
13	Hardness tester	Pharmatest	PTB-311E
14	Friabilator (USP)	Electro lab	EF-2
15	Compression machine	CLIT	CMP210
16	UV - Spectro photometer	ELICO	SL-164

2.3 Preparation of ciprofloxacin Tablets by wet granulation method

The tablets were prepared by wet granulation method. Ciprofloxacin and the polymer Gumkondagogu was mixed uniformly. CMC and starch was added to the drug and polymer mixture and blended thoroughly for 5 minutes. PVP K30 was dissolved in sufficient quantity of iso propyl alcohol and was added to the drug, polymer and lactose mixture to form a coherent mass. Then the formed coherent mass was sieved manually through sieve no. 16 to form granules. Then the granules are collected and dried at 400C for 2 hours. The dried granules were passed through sieve no. 20. The granules are then subjected to preformulation studies. After preformulation studies, the gran-

ules were mixed with magnesium stearate uniformly and are compressed into tablets

Table No. 3: Formula of CR Tablets containing Ciprofloxacin, and Gumkndagogu as polymer with different ratio

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Ciprofloxacin	100	100	100	100	100	100
Gumkondagogu	25	50	75	100	125	150
Carboxy methyl cellulose	10	10	10	10	10	10
Starch	335	310	285	260	235	210
Poly vinyl pyrolidine K30	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s

***Weight of each tablet was 500 mg**

2.4 Evaluation of Granules:

2.4.1 Angle of repose

Angle of repose (θ) was determined using fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface. Angle of repose was calculated using the following equation.

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

Where,

h and r are the height and radius as of cone respectively.

Table No: 4 Flow properties and Angle of repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair-aid not needed	36–40
Passable-may hang up	41–45
Poor-must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2.4.2Bulk density:

Bulk density is the ratio between a mass of granules and its bulk volume. It is expressed by g/cc. Bulk density was calculated using the following equation.

Bulkdensity = Weight of powder / Bulk volume

2.4.3 Tapped density:

Tapped density is the ratio between a mass of granules and volume of the granules after tapping. It is expressed by g/cc. Tapped density was calculated using the following equation.

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Final volume after tapping}}$$

2.4.4 Bulkiness:

Bulkiness is the reciprocal of bulk density. It is expressed by cc/g.

Bulkiness = 1/ Bulk density

2.4.5 Compressibility index and Hausner ratio:

The compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting granules flow characteristics. The compressibility index and Hausner ratio were determined by measuring both the Bulk density and tapped density of granules.

Compressibility index and Hausner ratio was calculated using the following equation.

$$\text{Compressibility index} = \frac{\text{TD - BD}}{\text{TD}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table No: 5 Carr's index & Hausner's ratio

Compressibility Index (%)	Flow Character	Hausner Ratio
10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

2.5 Evaluation of Tablets:

2.5.1 Hardness:

The strength of tablet is expressed as tensile strength (kg/cm2). The tablet-crushing load, which is the force, required breaking tablet by compression. It was measured using a tablet hardness tester (Pfizer Hardness Tester).

2.5.2 Weight variation:

Twenty tablets ware randomly selected and individually weighted. The average weight of tablets was calculated.

2.5.3 Friability:

Ten tablets were placed in the Roche friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dedusted and reweighed. Percentage friability was calculated by the following formula.

$$\text{Percentage Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

2.5.4 Estimation of drug content:

Ten tablets from each formulation were powdered. The powder equivalent to 100 mg of ciprofloxacin was weighed and dissolved in phosphate buffer pH 7.4 suitable dilutions was prepared and the solution was analyzed in UV-double beam spectrophotometer at 278nm using pH 7.4 as blank.

2.5.5 Thickness:

Thickness of the tablet was tested using vernier caliper(Besto).

2.6 FT-IR Spectral analysis:

The physicochemical compatability between Ciprofloxacin and gumkondagogu were carried out by subjecting to IR spectral studies using Perkin Elmer FTIR Spectrophotometer.The samples were scanned under diffuse reflectance mold and the graph was plotted by KBr pellet method and spectra were recorded in the wavelength region between 4000 cm-1 to 400 cm-1.The spectra obtained for ciprofloxacin,gumkondagogu and physical mixture of ciprofloxacin and gumkondagogu were compared.

2.7 Standard Calibration Curve of Ciprofloxacin:

100 mg of ciproflxacin was dissolved in 100ml of methanol. From this stock solution, 10 ml was withdrawn and further diluted to 100 ml with phosphate buffer pH 6.8 to obtain a concentration of 100 µg/ml. Aliquots of 2, 4,6, 8 and 10 ml were pipetted out and made up to 10ml with phosphate buffer pH 6.8 in order to obtain a concentration range of 2-10 µg/ml. The absorbance's of the solutions were measured at 278 nm by using UV-Vis spectrophotometer. A graph of Concentration Vs. Absorbance was plotted.

3.8 In vitro Release Studies:

In vitro Release Studies for all the formulated tablets were carried out using USP II paddle method at 50 rpm in 900 ml of pH 7.4 buffer solution as a dissolution medium, The dissolution medium was maintained at 370 ± 0.5 0C.10 ml of dissolution medium was withdrawn every 60 minutes intervals for 12 hrs. 10 ml of buffer solution (pH 7.4) was replaced to maintain the constant volume throughout the experiment. The percentage of ciprofloxacin released from each formulation was measured at 278 nm using UV-visible spectrophotometer (Elico-SL164). Results of in vitro drug release studies obtained from absorbance data were tabulated and shown graphically as cumulative percentage drug released vs. Time.

The results obtained of in vitro release studies were attempted to fit into various mathematical models as follows:

1. Cumulative percent drug released Vs. Time (Zero order rate kinetics).
2. Log Cumulative percent drug retained Vs. Time (First order rate kinetics).
3. Cumulative percent released Vs. √T [Higuchi's classical diffusion equation (Higuchi matrix)].
4. Log of cumulative percent drug released Vs. Log Time (Peppas exponential equation).
5. $(\text{Percentage Retained})^{1/3}$ Vs. Time (Hixson-Crowell erosion equation).

Zero order rate equation describes that system where the release rate is independent of the concentration of the dissolved species. The first order equation describes the release from systems where dissolution rate is dependent on the concentration of dissolving species. The Higuchi square root equation describes the release from systems, where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion. The Hixson – Crowell cube root law describes the release from system where there is a change in surface area and diameter of the particles (or) tablets. Peppas – Korsmeyer equation is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. The 'n' value could be used to characterize different release mechanisms.If than value below 0.5 fickaninan diffusion, $0.5 < n < 1$, Non-Fickian diffusion and n=1 zero order release mechanism.

3. RESULTS & DISCUSSIONS

In the present study, ciprofloxacin controlled release matrix tablets were prepared by using, the natural polymer Gumkondagogu in different ratios (1:0.25, 1:0.50, 1:0.75,1:1, 1:1.25,1:1.50). A total number of six formulations were prepared by wet granulation method.

3.1 Evaluation of granules

Table No 6: Evaluation of granules

Formulation	Angle of Repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Bulkiness(cc/g)	Compressibility index (%)	Hausners ratio
F1	31.36 ±0.312	0.367 ±0.012	0.416 ±0.025	2.72 ±0.032	11.77 ±0.209	1.13 ±0.132
F2	33.39 ±0.632	0.347 ±0.025	0.396 ±0.034	2.88 ±0.041	12.37 ±0.404	1.14 ±0.256
F3	33 .74 ±0.321	0.351 ±0.026	0.401 ±0.043	2.84 ±0.062	12.46±0.391	1.14 ±0.221
F4	32. 96 ±0.729	0.349 ±0.037	0.396 ±0.033	2.89 ±0.052	11.86 ±0.227	1.13 ±0.312
F5	33. 28 ±0.271	0.357 ±0.022	0.396 ±0.030	2.80 ±0.054	10.89 ±0.322	1.10 ±0.109
F6	31. 96 ±0.302	0.354 ±0.045	0.401 ±0.056	2.49±0.066	11.72 ±0.211	1.13 ±0.210

All the reading are expressed as mean ± standard deviation (n=3)

Angle of repose for F1- F6 is between 30-35, bulk density is between 0.347-0.367, tapped density is between 0.396-0.401, bulkiness is between 2.49-2.89, compressibility index is between 10.89-12.46 is with in the acceptable limits, and hausners ratio is between 1.10-1.14. The above values of pre compression parameters shows the prepared granules having good flow property.

3.2 Evaluation of CR tablets of Ciprofloxacin

Table No.7 Evaluation of CR tablets of ciprofloxacin

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Thickness (mm)
F1	497 ±2.6	5.12 ±0.16	0.512 ±0.06	97.5 ±0.36	4.3 ±0.04
F2	496 ±3.1	5 .35±0.33	0.516 ±0.19	97.7±0.21	4.2 ±0.04
F3	498 ±2.8	4.99 ±0.20	0.601 ±0.09	97.1 ±0.41	4.2±0.03
F4	498 ±3.7	5.08±0.47	0.596 ±0.33	96.9 ±0.26	4.3 ±0.05
F5	495 ±4.3	4.99 ±0.32	0.454 ±0.16	98.3±0.31	4.1±0.02
F6	497 ±4.5	5.10 ±0.22	0.493 ±0.27	97.1 ±0.19	4.2 ±0.07

Weight variation was within ±5% it was within the acceptable limit , hardness was with in 4-10 was within the acceptable limits, friability was within 1% it was within the limit, drug content was within 90-110 it was within the acceptable limits, all formulations showed uniform thickness.

3.3 Compatbility studies

Infra-red (IR) spectroscopy was used as means of studying drug – polymer compatibility and confirmed by comparing undisturbed structure of IR spectra of Ciprofloxacin, which indicated no drug- polymer interaction.

Table No 8: Comparison of IR Spectra of Ciprofloxacin & physical mixture of Ciprofloxacin, Gumkondagogu

S. No.	Material	Peaks (cm^{-1})	Characteristic functional groups
1	Ciprofloxacin	1. 1623.83 2. 1448.73-1494.56 3. 1269.86-1340.35 4. 3378.01 5. 3529.00	ketone C = O str. Aromatic C = C str. C – N str O-H str (carboxylic acid) N-H str (secondary amine)
2	Physical mixture of ciprofloxacin and gumkondagogu	1. 1623.63 2. 1449.93-1497.08 3. 1270.51-1342.04 4. 3383.37 5. 35297.88	ketone C = O str. Aromatic C = C str. C – N str O-H str (carboxylic acid) N-H str (secondary amine

From the above table it was concluded that there were no changes in the peak shape and no shift of peaks. So both the drug and excipients were compatible. FTIR spectra of pure drug ciprofloxacin, gumkonda-

gogu and physical mixture of ciprofloxacin and gumkondagogu are shown in Fig. 1, 2 and 3.

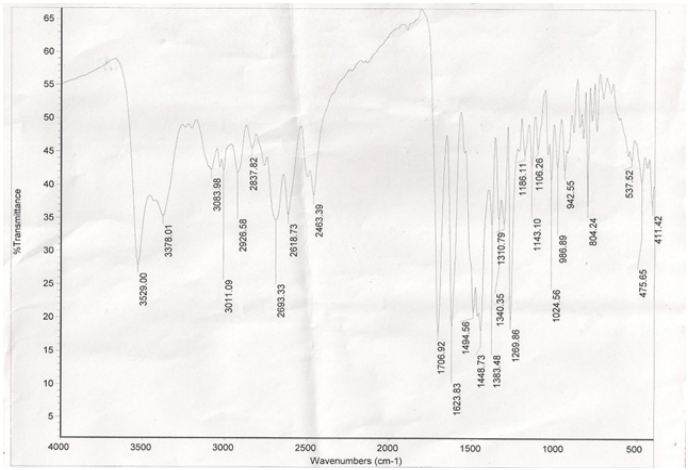


Fig 1: IR Spectrum of Ciprofloxacin

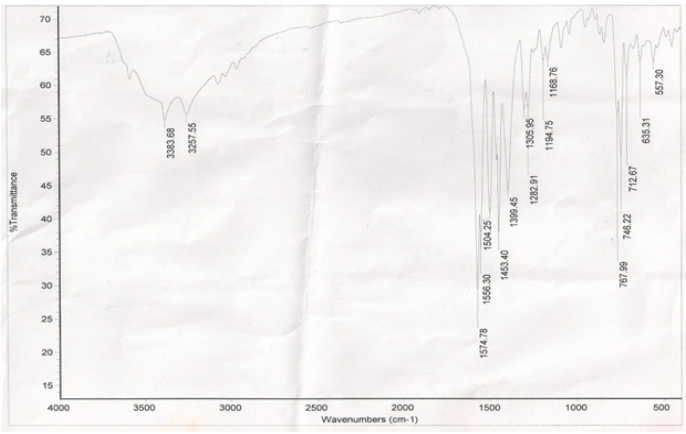


Fig 2: IR Spectrum Of Gumkondagogu

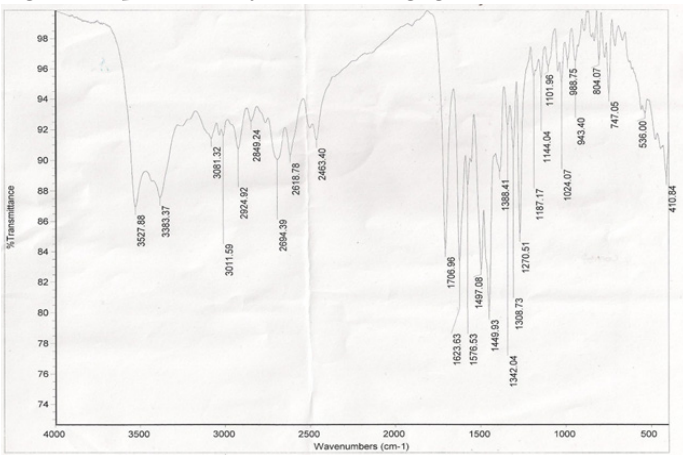


Fig 3: IR Spectrum of Physical mixture of Ciprofloxacin & Gumkondagogu

3.4 Standard calibration curve of ciprofloxacin by UV spectrophotometry

An UV spectrophotometric method based on the measurement of absorbance at 278 nm in phosphate buffer pH 7.4 was used for estimation of ciprofloxacin. A standard curve from the stock solution was obtained in the range of 2-10 µg/ml concentration using phosphate buffer pH 6.8 by measuring absorbance at 278 nm.

Table 9 shows the absorbance of ciprofloxacin standard solutions containing 2-10 µg/ml of drug in phosphate buffer pH 7.4.

Table No. 9: Calibration data of Ciprofloxacin in phosphate buffer at pH 7.4

S. No.	Concentration (µg/ml)	Absorbance*
1	0	0
2	2	0.035
3	4	0.066
4	6	0.103
5	8	0.141
6	10	0.169

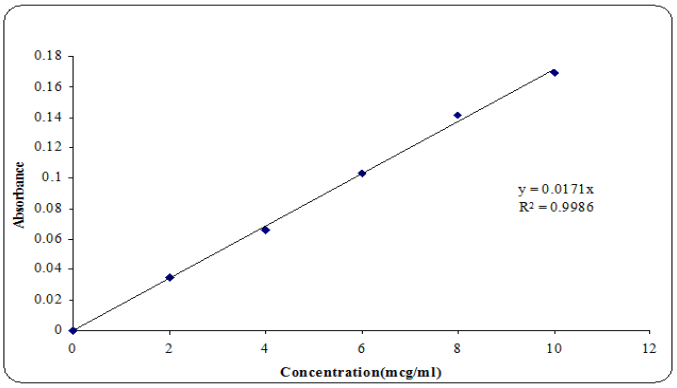


Figure 4: shows a representative standard calibration curve with slope 0.017 and regression value of 0.9986. The curve was found to be linear in the range of 2-10 µg/ml at λ_{max} 278 nm.

The calculation of the drug content and in-vitro release are based on this and similar calibration curves.

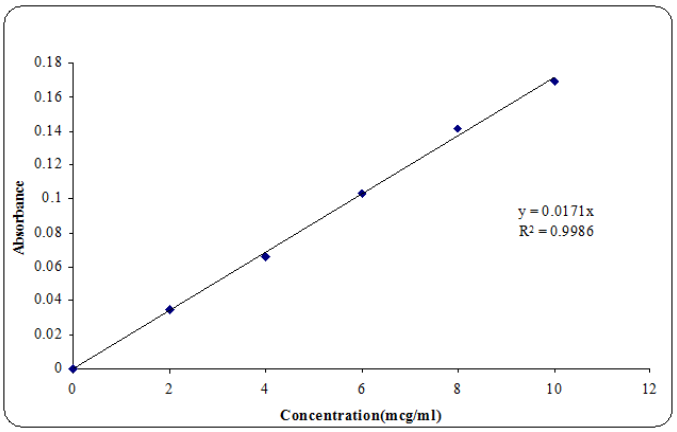


Fig. 5 Standard calibration curve for ciprofloxacin in 7.4 pH at λmax 278 nm.

The linear regression analysis was done on absorbance data points. The results are as follows:

The Slope = 0.017
The intercept = 0
The correlation coefficient = 0.9986

A straight-line equation (y = mx + c) was generated to facilitate the calculation for amount of drug. The

equation is as follows.

Absorbance = 0.017 X Concentration

3.5 In vitro release studies:

The release data obtained for formulations F-1 to F-6 are tabulated in Table 10 to 16. The in vitro release study showed that if the polymer ratio is increased, then the release of the drug is prolonged.

TableNo: 10 In vitro dissolution profile of ciprofloxacin from formulation F1

Time (min)	Sq root of time	Log time	Absorbance	Conc Mcg/ml	Conc in 900ml (Mg)	% drug Release	Log CDR	% Drug remaining	Log % drug remaining	Cube root of % drug remaining
1	1	0	0.025	1.49	13.46	13.46	1.120	86.54	1.937	4.423
2	1.414	0.3010	0.037	2.21	19.94	19.94	1.299	80.06	1.903	4.309
3	1.732	0.4771	0.044	2.60	23.42	23.42	1.369	76.58	1.884	4.246
4	2.0	0.6020	0.052	3.11	28.03	28.03	1.447	71.97	1.857	4.156
5	2.236	0.6989	0.070	4.12	37.16	37.16	1.570	62.84	1.798	3.975
6	2.449	0.7781	0.086	5.06	45.60	45.60	1.658	54.40	1.735	3.789
7	2.645	0.8450	0.117	6.93	62.41	62.41	1.795	37.59	1.575	3.349
8	2.828	0.9030	0.014	8.35	75.16	75.16	1.875	24.84	1.395	2.917
9	3	0.9542	0.162	9.56	86.12	86.12	1.935	13.88	1.142	2.403
10	3.162	1	0.188	11.08	99.72	99.72	1.994	1.28	0.107	1.085

Table No 11: In vitro dissolution profile of ciprofloxacin from formulation F-2

Time (min)	Sq root of time	Log time	Absorbance	Conc Mcg/ml	Conc in 900ml (Mg)	% drug Release	Log CDR	% Drug remaining	Log % drug remaining	Cube root of % drug remaining
1	1	0	0.023	1.38	12.50	12.50	1.096	87.50	1.942	4.439
2	1.414	0.3010	0.033	1.993	17.94	17.94	1.254	82.06	1.914	4.345
3	1.732	0.4771	0.040	2.380	21.42	21.42	1.330	78.58	1.895	4.283
4	2.0	0.6020	0.051	3.006	27.06	27.06	1.432	72.94	1.862	4.178
5	2.236	0.6989	0.066	3.912	35.21	35.21	1.546	64.79	1.811	4.016
6	2.449	0.7781	0.081	4.795	43.16	43.16	1.635	56.84	1.754	3.844
7	2.645	0.8450	0.107	6.347	57.13	57.13	1.756	42.87	1.632	3.499
8	2.828	0.9030	0.125	7.354	66.19	66.19	1.820	33.81	1.524	3.230
9	3.00	0.9542	0.143	8.460	76.14	76.14	1.881	23.86	1.377	2.878
10	3.162	1.00	0.172	10.17	91.6	91.6	1.961	8.40	0.924	2.032
11	3.316	1.042	0.187	11.05	99.45	99.45	1.997	0.55	-0.251	0.819

Table No 12: In vitro dissolution profile of ciprofloxacin from formulation F-3

Time (min)	Sq root of time	Log time	Absorbance	Conc Mcg/ml	Conc in 900ml (Mg)	% drug Release	Log CDR	% Drug remaining	Log % drug remaining	Cube root of % drug remaining
1	1	0	0.021	1.288	11.60	11.60	1.064	88.40	1.946	4.454
2	1.414	0.3010	0.030	1.804	16.24	16.24	1.210	83.76	1.923	4.375
3	1.732	0.4771	0.036	2.134	19.21	19.21	1.283	80.79	1.907	4.323
4	2.0	0.6020	0.047	2.802	25.22	25.22	1.401	74.78	1.873	4.213
5	2.236	0.6989	0.062	3.681	33.13	33.13	1.520	66.87	1.825	4.058
6	2.449	0.7781	0.075	4.427	39.85	39.85	1.600	60.15	1.779	3.918
7	2.645	0.8450	0.094	5.574	50.17	50.17	1.700	49.83	1.697	3.679

8	2.828	0.9030	0.121	7.128	64.16	64.16	1.807	35.84	1.554	3.297
9	3.00	0.9542	0.141	8.312	74.81	74.81	1.873	25.19	1.401	2.931
10	3.162	1.00	0.164	9.668	87.02	83.02	1.939	12.98	1.113	2.350
11	3.316	1.042	0.174	10.27	92.5	92.5	1.966	7.50	0.875	1.957
12	3.464	1.079	0.187	11.05	99.47	99.47	1.997	0.53	-0.27	0.809

Table No 13: In vitro dissolution profile of ciprofloxacin from formulation F-4

Time (min)	Sq root of time	Log time	Absorb ance	Conc Mcg/ ml	Conc in 900ml (Mg)	% drug Release	Log CDR	% Drug remaining	Log % drug remaining	Cube root of % drug remaining
1	1.000	0	0.020	1.222	11.00	11.00	1.041	89.00	1.949	4.464
2	1.414	0.3010	0.026	1.578	14.21	14.21	1.152	85.79	1.933	4.410
3	1.732	0.4771	0.033	1.962	17.66	17.66	1.246	82.34	1.915	4.350
4	2.000	0.6020	0.043	2.581	23.23	23.23	1.366	76.77	1.885	4.250
5	2.236	0.6989	0.055	3.240	29.16	29.16	1.464	70.84	1.850	4.137
6	2.449	0.7781	0.068	4.015	36.14	36.14	1.557	63.86	1.805	3.997
7	2.645	0.8450	0.085	5.024	45.22	45.22	1.655	54.78	1.738	3.797
8	2.828	0.9030	0.106	6.273	56.46	56.46	1.751	43.54	1.638	3.518
9	3.000	0.9542	0.131	7.760	69.84	69.84	1.844	30.16	1.479	3.112
10	3.162	1.000	0.155	9.122	82.1	82..10	1.924	15.97	1.203	2.581
11	3.316	1.042	0.170	10.02	90.19	90.19	1.965	9.81	0.991	2.140
12	3.464	1.079	0.185	10.93	98.43	98.43	1.993	1.57	0.199	1.162

Table No 14: In vitro dissolution profile of ciprofloxacin from formulation F-5

Time (min)	Sq root of time	Log time	Absorb ance	Conc Mcg/ ml	Conc in 900ml (Mg)	% drug Release	Log CDR	% Drug remaining	Log % drug remaining	Cube root of % drug remaining
1	1	0	0.017	1.022	9.2	9.2	0.963	90.80	1.958	4.494
2	1.414	0.3010	0.025	1.476	13.29	13.29	1.123	86.71	1.938	4.426
3	1.732	0.4771	0.028	1.695	15.26	15.26	1.183	84.74	1.928	4.392
4	2.0	0.6020	0.041	2.445	22.01	22.01	1.342	77.99	1.892	4.272
5	2.236	0.6989	0.052	3.074	27.67	27.67	1.442	72.33	1.859	4.166
6	2.449	0.7781	0.066	3.884	34.96	34.96	1.543	65.04	1.813	4.021
7	2.645	0.8450	0.079	4.687	42.19	42.19	1.614	57.81	1.762	3.866
8	2.828	0.9030	0.104	6.122	55.10	55.10	1.741	44.90	1.652	3.554
9	3	0.9542	0.129	7.625	68.63	68.63	1.836	31.37	1.496	3.153
10	3.162	1	0.151	8.89	80.01	80.01	1.903	19.99	1.300	2.713
11	3.316	1.042	0.166	9.79	88.12	88.12	1.945	11.88	1.074	2.281
12	3.464	1.079	0.184	10.84	97.61	97.61	1.989	2.39	0.378	1.337

Table No 15: In vitro dissolution profile of ciprofloxacin from formulation F-6

Time (min)	Sq root of time	Log time	Absorb ance	Conc Mcg/ ml	Conc in 900ml (Mg)	% drug Release	Log CDR	% Drug remaining	Log % drug remaining	Cube root of % drug remaining
1	1.000	0	0.014	0.833	7.5	7.5	0.875	92.5	1.966	4.522
2	1.414	0.3010	0.021	1.240	11.16	11.16	1.047	88.84	1.948	4.462
3	1.732	0.4771	0.026	1.532	13.79	13.79	1.139	86.21	1.935	4.417

4	2.000	0.6020	0.037	2.217	19.96	19.96	1.300	80.04	1.903	4.309
5	2.236	0.6989	0.045	2.670	25.03	25.03	1.398	74.97	1.874	4.216
6	2.449	0.7781	0.056	3.351	30.16	30.16	1.479	69.84	1.844	4.118
7	2.645	0.8450	0.074	4.384	39.46	39.46	1.596	60.54	1.782	3.926
8	2.828	0.9030	0.091	5.380	48.42	48.42	1.685	51.58	1.712	3.722
9	3.000	0.9542	0.111	6.573	59.16	59.16	1.772	40.84	1.611	3.443
10	3.162	1.000	0.134	7.906	71.16	71.16	1.852	28.84	1.459	3.066
11	3.316	1.042	0.159	9.37	84.33	84.33	1.925	15.67	1.195	2.502
12	3.464	1.079	0.173	10.18	91.64	91.64	1.962	8.36	0.922	2.09
13	3.605	1.113	0.188	11.07	99.67	99.67	1.998	0.33	-0.481	0.691

The % drug release was found to have the influence of Natural polymer employed in the preparation of tablets. Good correlation has been observed between the concentration of polymer and % drug release.It could arise because of increased viscosity of dissolution media with the increased concentration of Natural polymer. The in vitro release study showed that if the polymer ratio is increased, then the release of the drug is prolonged.

3.6 Drug Release kinetics

Plots of zero order, first order, Higuchi matrix, Peppas and Hixson Crowell are depicted in Figure 6 to 10. The regression coefficient (r) and 'n' values for formulations (F-1 toF-6) of zero order, first order, Higuchi matrix, Peppas and Hixson-Crowell are tabulated in Table. No. 14.

Fig. 6 Zero order Plot of Gumkondagogu, Ciprofloxacin Controlled release Matrix tablets(F1-F6)

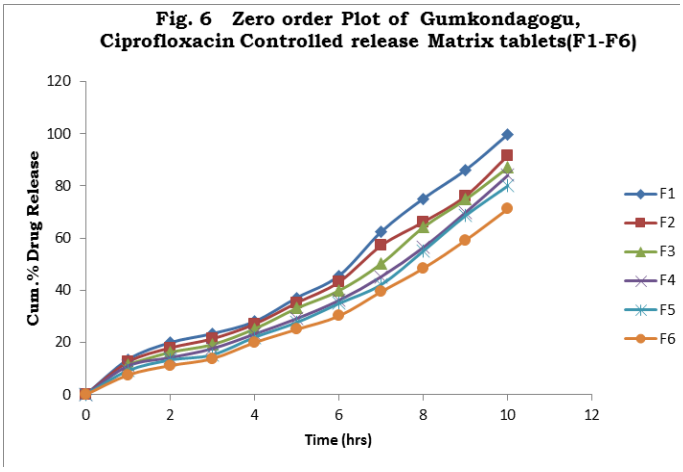


Fig 8 Higuchi Plot of Gumkondagogu,Ciprofloxacin Controlled release Matrix tablets

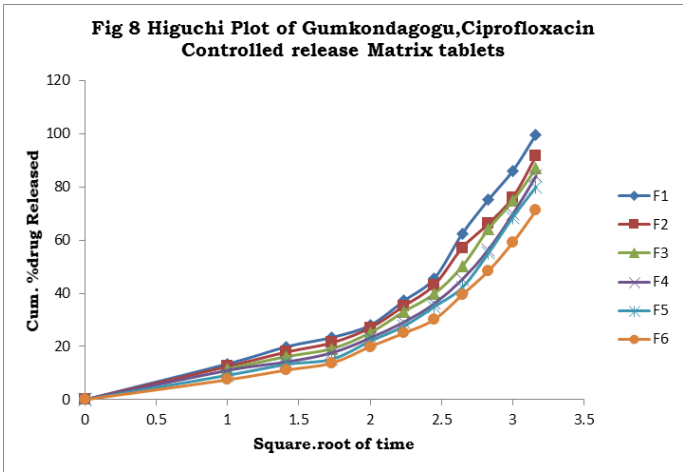


Fig. 7 First order Release Plot of Gumkondagogu,Ciprofloxacin Controlled release Matrix tablets

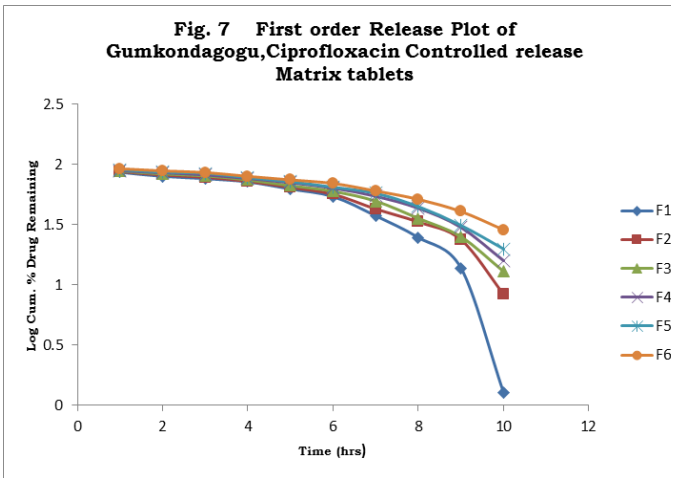


Fig. 9 Korsmeyer Peppas Plot of Gumkondagogu,Ciprofloxacin Controlled release Matrix tablets

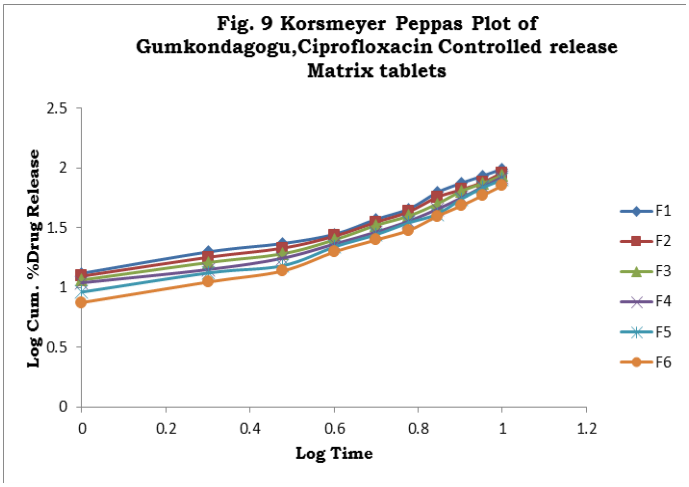
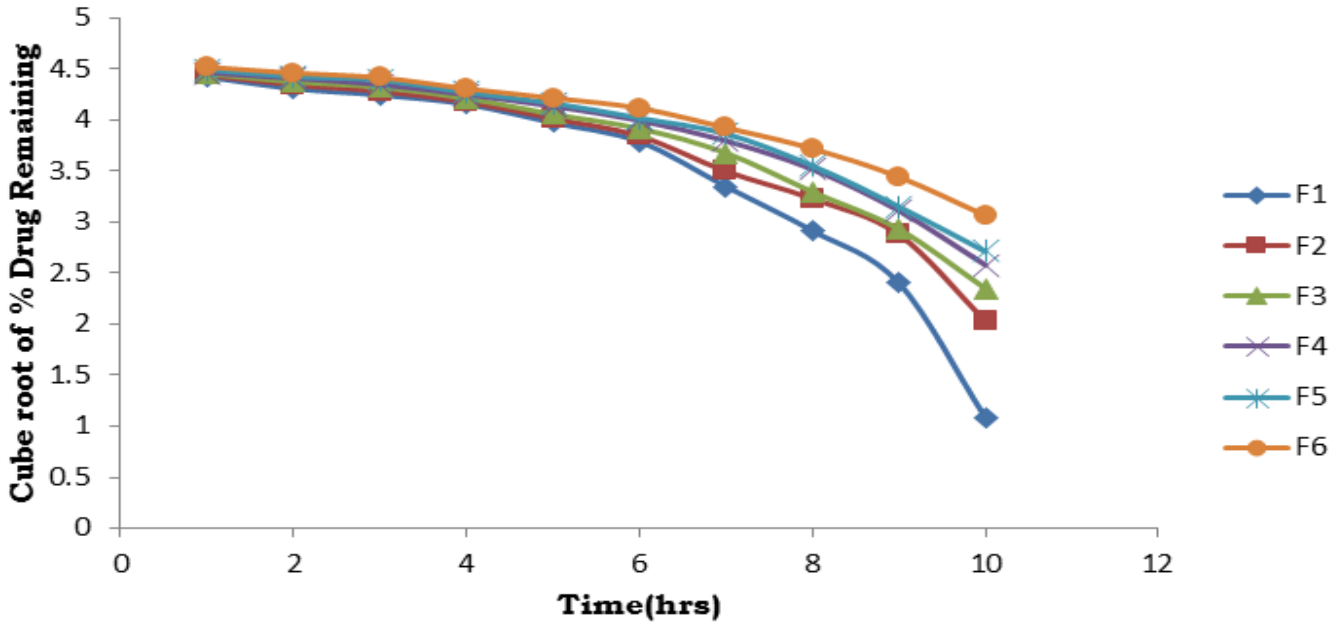


Fig. 10 Hixson-crow well Plot of Gumkondagogu,Ciprofloxacin Controlled release Matrix tablets



The drug release data obtained were extrapolated by Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations.These results indicate that zero order plots were linear for all formulations and the first order plots were not linear for all formulations.

The in vitro release profiles of drug from F1 to F6 formulations could be best expressed by Zero equation as the plots showed highest linearity (R2: 0.934 to 0.968). It confers that drugs are released by diffusion. To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. All the formulations showed good linearity (0.922 to 0.950) with slope (n) values ranging from 0.88 to 0.99 indicating that diffusion was the predominant mechanism of drug release from these formulations indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.99$).

Figure 4.7 shows the graphical representation of cumulative percent drug released as a function of square root of time. This Higuchi's plot was not linear with poor regression co-efficient values .

Hixson Crowell plot. of the formulations is indicated in Figure 4.9. The regression coefficients of formulations F1 to F6 were in the range (R2 0.824-0.908) and found to be not linear.

The release profile of Ciprofloxacin from all these formulations (F1-F6) displayed good fitting with Korsmeyer-Peppas model of drug release, confers that diffusion was the predominant mechanism of drug release.

Table No. 14: Curve fitting data for all tablet formulations (F1-F6)

Formulations	Zero order Equation		First order Equation		Higuchi's Equation		Peppas Equation		Hixson-crow Well Equation	
	n	R^2	n	R^2	n	R^2	n	R^2	n	R^2
F1	9.549	0.968	-0.152	0.673	30.91	0.840	0.896	0.935	-0.319	0.824
F2	8.589	0.974	-0.094	0.800	27.91	0.851	0.882	0.943	-0.238	0.877
F3	8.455	0.961	-0.081	0.835	34.75	0.889	0.901	0.935	-0.217	0.890
F4	7.792	0.934	-0.071	0.812	24.82	0.814	0.901	0.922	-0.192	0.876
F5	7.545	0.954	-0.065	0.842	24.16	0.810	0.958	0.932	-0.184	0.885
F6	6.688	0.961	-0.051	0.876	21.45	0.818	0.992	0.950	-0.151	0.908

n=slope

R2=regression coefficient

CONCLUSION

From the data obtained, it can be concluded that:

- Development of controlled release formulation of ciprofloxacin can be advantageous to provide prolonged and increase the efficacy of the dosage form, there by improve bioavailability of the drug.
- The Natural polymer (Gum Kondagogu) selected as the polymer is more reliable as it released the drug slowly, extending the release over a longer period of time.
- Formulated tablets gave satisfactory results for various physical properties for tablets like tablet thickness, hardness, weight variation, friability, content uniformity and in vitro drug release.
- Formulated tablets best fitted to Korsmeyer-Peppas model and zero order kinetics..
- Thus the objective of formulating a controlled release dosage forms of ciprofloxacin by Natural polymer.

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