A REVIEW ON CIPROFLOXACIN: DOSAGE FORM PERSPECTIVE

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ABSTRACT

Ciprofloxacin (CF) is one of the topmost selling antibiotics and it is available at a cheap cost which is used to treat many bacterial infections. Many research scientists are working on this drug for various applications on different drug delivery systems. The main objective of this paper is to enlighten about the details of pure drug CF and its delivery systems along with current research on this drug. This review focused on history, pharmacokinetics, mechanism of action, types of dosage form available in the market with their cost, current research going on this drug with their patents available. The present review revealed that the only analytical method for estimation of CF was developed in the first decade, few drug delivery systems (DDS) of CF were developed in the second decade and more research work on the development of novel DDS of CF founded in the last decade.

Keywords: Ciprofloxacin, Drug delivery systems, Analytical methods

INTRODUCTION

Ciprofloxacin (CF) is an antibacterial which is available at a cheap cost [1] and used to treat many bacterial infections [2]. It belongs to fluoroquinolones category and is a broad spectrum second generation antibacterial agent [3]. It is mostly used to treat gram negative bacterial infections, urinary tract infections, skin, ophthalmic, respiratory, bone and joint, intraabdominal infections bacterial diarrheal infections [4] and periodontal pathogens [5]. But it is not effective against viral diseases. It is a nucleic acid synthesis inhibitor [6]. It is one of the topmost selling antibiotics [1] and numbers of researchers are working with this drug for different applications or improvements in its applications.

Hence, the search criteria used in the present review were the research work on the development of novel drug delivery systems of CF in the last 3 decades (1985-2017) including the patents and different marketed products of CF with their price along with the properties and uses of CF. Properties [7] of CF are shown in table 1 and the storage temperatures required for different dosage forms is between 5-25 ºC [8].

| Name of property | Description | Reference number |
|------------------|-------------|------------------|
| State            | Solid       |                  |
| Water solubility | 1.35 mg/ml  | 7                |
| Melting point ( ºC) | 255-257    |                  |
| Log P            | -0.57       |                  |
| pKa (Strongly Acidic) | 5.76        |                  |
| pKa (Strongest Basic) | 8.68        |                  |
| Biological half-life | 3.5 h      |                  |

History

Quinolones were first developed in 1960’s, then they were classified into generations based on antimicrobial activity. In the first generation, nalidixic acid was developed in 1962 to treat urinary tract infections and later in 1980 by insertion of F atom in quinolone ring a 2nd generation CF was developed to treat a number of infections [9].

Pharmacokinetic parameters

The pharmacokinetic parameters of CF are listed in table 2

Absorption

60-80% CF is rapidly absorbed with tmax of 1 to 1.5 h, when given by oral route and it has no significant effect when administered with food, but altered with ingestion of sucralfate, FeSO4 and antacids [7].

Distribution

It penetrates well into the most of the body fluids and tissues. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genitalic tissue, including the prostate [3].

Metabolism

It is metabolized into oxoCF, sulfoCF and other active metabolites. On oral administration, approximately 15% of the dose is converted into four metabolites identified in human urine which are less active than unchanged CF [8].

Elimination

50% of CF are eliminated by kidney, 15% by feces, and 45% of liver and other intestinal mucosal secretions [3].

USES/Indication

CF is used to treat acute sinusitis, lower respiratory tract infection, chronic bronchitis, hospital acquired pneumonia, kidney, urinary tract, diarrheal and abdominal infections, skin and soft tissue, bone and joint infections, acute otitis and uncomplicated cystitis and gonorrhea.

Mechanism of action

The fluoroquinolones act by inhibiting type 2 bacterial DNA topoisomerases, DNA gyrase and topoisomerase IV. They bind and

Table 1: Properties of ciprofloxacin
trap the enzyme-DNA complex [6]. This blocks DNA synthesis and cell growth and ultimately shows a lethal effect on the cell [7].

Different mechanisms of actions of CF against different organisms are shown in table 3.

| Table 2: Pharmacokinetic parameters |
|-------------------------------------|
| Parameter                           | Values          | Reference number |
| Half life                           | 3 to 4 h        |                 |
| Bioavailability (Oral)              | 6%              | 3,7,8           |
| Renal excretion                     | 70 %            |                 |
| Plasma protein binding              | 30%             |                 |
| Volume of distribution              | 2/3.5 L/kg      |                 |
| Hepatic metabolism                 | 5%              |                 |

| Table 3: List of target enzymes of different organisms inhibited by ciprofloxacin |
|------------------------------------------|
| Target enzyme                            | Organism                  | Reference number |
| DNA topoisomerase 4 subunit 4 A          | Haemophilus influenza, Staphylococcus aureus | 6,7              |
| DNA topoisomerase 2-alpha and K-voltage-gated channel subfamily H member | Human |  |
| DNA gyrase subunit A                     | Haemophilus influenzae, Escherichia coli (strain K12), Bacillus subtilis (strain 168), Staphylococcus aureus |  |
| DNA topoisomerase 4 subunit 4 B          | Bacillus subtilis (strain 168) |  |
| Multidrug resistant protein MdtK         | Escherichia coli |  |

Dosage forms
CF is available in the market as tablet, infusion, eye drops, suspensions, ointments with varying cost prepared by a number of companies to treat various bacterial infections. Table 4 illustrated the number of dosage forms of CF available with their cost range and number of companies manufacturing these CF dosage forms [10].

| Table 4: Different dosage forms of ciprofloxacin available in the market with cost |
|------------------------------------------|
| Dosage form                | Available number | Cost range (Rs) | Number of manufacturing companies | Reference number |
| Tablets                  | 214              | 8-125/10 tablets | 98 |  |
| Infusion                 | 17               | 17.86/-/100 ml  | 14 | 10 |
| Eye drops                | 28               | 6-2480/10 ml    | 24 |  |
| Suspensions              | 4                | 27.76-48.50/60 ml | 4 |  |
| Ointments               | 4                | 4.31-10/5 ml    | 4 |  |

Table 5: Different drug delivery systems of ciprofloxacin developed

| Type of drug delivery system | Name of formulation | Application                                      | Reference number |
|-----------------------------|---------------------|-------------------------------------------------|------------------|
| Gastros retentive floating DDS | Tablets            | To achieve the controlled release of the drug   | 13               |
| Ophthalmic DDS             | In-situ gel         | To achieve sustained drug release               | 14               |
| Cutaneous wound closures   | Hydrogels           | To treat the wounds infected by *pseudomonas aeruginosa* | 17               |
| Controlled release DDS     | Films               | To treat periodontitis                          | 16               |
| Gastros retentive sustained release DDS | Microbeads       | To Prolong duration of action                    | 19               |
| Targeted DDS               | Elastic liposomes   | To treat acne vulgaris                          | 20               |
| Sustained release DDS      | Floating matrix tables | To extend absorption of CF,                     | 21               |
| Sustained release DDS      | Tablets             | To prolong the drug release                     | 22               |
| Controlled DDS             | Dental films        | To treat periodontitis                          | 23               |
| Ophthalmic DDS             | Ocular Inserts      | To treat ocular conjunctivitis                  | 24               |
| Wound closures             | Composite films     | For wound healing                               | 25               |
| Floating bioadhesive DDS   | Tablets             | To increase the stay period of drug in its absorption area and to decrease the dosing interval | 26               |
| Swellable and gastro-retentive DDS | Tablets       | To prolong gastric emptying time                | 27               |
| Topical DDS                | Films               | To treat periodontitis                          | 28               |
| Ophthalmic DDS             | In-situ gel         | To treat eye infections like dacrocystitis, bacterial conjunctivitis corneal ulceration | 29               |
| Multi-unit floating DDS    | Beads               | To know about the effect of additives           | 30               |
| Extended-release DDS       | Tablets             | To Prolong duration of the release              | 31               |
| The novel vesicular carrier system | Niosomal cream | To improve skin retention and prolong the local effect on skin | 32               |

Patents filed/Sanctioned
As per FDA, 12 patents are found in literature for different products or activities and also a list of 20 patents are given in the drug bank [11, 12].

Current research on ciprofloxacin
Development of drug delivery systems (DDS)
As CF is a broad spectrum antibiotic it acts on a wide range of organisms and prescribed by many doctors, the present review work on CF is undertaken. The research work was conducted on this drug to improve its applications in different diseased conditions by many scientists. Most of the research work was carried out to formulate liposomes, films, niosomal creams, gastro-retentive tablets, hydrogels, dental films, ocular inserts, and microbeads. It is also used to treat acne vulgaris which is a common chronic disease of the sebaceous follicles in the form of the liposome drug delivery system. The gastro-retentive tablets were formulated to improve absorption of the drug as it has a narrow absorption window. Likewise, it is used to treat periodontitis, which is effective against...
Analytical methods for estimation of ciprofloxacin

Several analytical methods for the quantitative determination of CF in pharmaceutical formulations were developed like electrophoresis, UV spectrophotometry, titration, and High-Performance Liquid Chromatography (HPLC). Quantification is necessary to determine the quality of medicine, which are available in the market.

Which are later used for quantification of CF in urine, plasma, animal tissue, and other samples. Methods developed for estimation of CF in different samples are given in table 6.

| Sample                        | Method             | Application                                                                 | Reference number |
|-------------------------------|--------------------|------------------------------------------------------------------------------|------------------|
| Body fluids                   | HPLC               | This method is ideal for clinical trials and PK studies of CF                | 30               |
| Biological fluids             | HPLC               | To study the pharmacokinetics of CF                                          | 31               |
| Plasma and urine              | HPLC               | Used to measure only the parent drug in human serum and urine but not metabolites | 32               |
| Pharmaceutical preparations   | RP-HPLC            | Separation of compounds and to determine the pharmacokinetics of CF         | 33               |
| and biological fluids         | HPLC               | Quantitative determination of 2nd generation quinolones                      | 34,35            |
| Pharmaceutical preparations   | HPLC               | The first derivative method is successfully applied (difficulty with excipients can overcome by selecting at appropriate wavelength) | 9                |
| Ophthalmic solution           | HPLC with UV detection | Highly efficient for quantification in matrices evaluated                     |                  |
| Serum and urine               | HPLC               | To study the pharmacokinetics of CF in patients receiving multiple drug therapy | 36               |

Interaction and reactions with ciprofloxacin

Two types of possible interactions were found, those are drug-drug and drug-food interaction as shown below.

Drug-drug interaction

As CF is an inhibitor of CYP 1A2, the drugs majorly metabolized by CYP 1A2 metabolized drugs have shown adverse reactions when administered along with CF [38]. They are around 275 drug interactions listed in drug bank [7]. But some drug interactions with CF based on drugs category and its effects are shown in table 7.

Drug-food interaction

CF, when taken with food, decreased the rate, but not the extent of absorption of CF [39]. List of food interactions with CF and its effects are shown in table 8.

| Category                                | Effect                                                                 | Reference number |
|-----------------------------------------|------------------------------------------------------------------------|------------------|
| Caffeine and xanthine derivative         | Reduced clearance of caffeine and a prolongation of its serum half-life | 7,37,38          |
| Class Ia or II Antiarrhythmics           | CF may have an additive effect on the QT interval                      |                  |
| Histamine H2-Receptor Antagonists        | No significant effect on the bioavailability of CF                     |                  |
| Multivalent Cations                      | Lower serum and urine levels                                           |                  |
| Nonsteroidal Anti-Inflammatory Drugs     | Increase the risk of central nervous system stimulation and convulsive seizures. |                  |
| (NSAIDs)                                | Increase in oral anticoagulant activity                               |                  |
| Oral Anticoagulants                     |                                                                        |                  |

| Category                                | Effect                                                                 | Reference number |
|-----------------------------------------|------------------------------------------------------------------------|------------------|
| Tablet                                  | Delay in the absorption of CF                                          | 39               |
| Suspension                              | No delay is observed                                                   |                  |
| Any formulation                         | Decrease in the absorption of CF                                       |                  |

| Organ/System name                       | ADR                                                                 | Reference number |
|-----------------------------------------|---------------------------------------------------------------------|------------------|
| CNS                                     | Nervousness, agitation, insomnia, anxiety, nightmares, dizziness, confusion, tremors, hallucinations, psychotic reaction, depression | 36,39,40         |
| CVS                                     | Orthostatic hypotension, Vasculitis                                  |                  |
| EYE                                     | Blurred vision, burning, stinging, irritation, itching, tearing, and redness of eyes, eyelid itching, swelling, or crustation, sensitivity to light |                  |
| GI System                               | Nausea, vomiting, diarrhea, constipation, abdominal pain or discomfort, dyspepsia, dysphagia, flatulence, pancreatitis, pseudomembranous colitis |                  |
| Urinary system                          |                                                                      |                  |
| Skin                                    | Rashes, exfoliative dermatitis, toxic epidermal necrolysis, erythema, Toxic epidermal necrolysis, Stevens-Johnson syndrome |                  |
| Hepatic system                          |                                                                      |                  |
| Musculoskeletal system                  |                                                                      |                  |
| Others                                  |                                                                      |                  |

Table 6: Analytical methods for estimation of Ciprofloxacin in different samples

Table 7: List of drug interactions of ciprofloxacin and its effects

Table 8: List of interactions with ciprofloxacin dosage forms and its effects

Table 9: Adverse drug reactions of ciprofloxacin
Adverse drug reactions (ADRs) of CF

CF use is associated with disabling and potentially irreversible serious adverse reactions [38, 39]. CF has also shown some adverse effects on different organs or systems of the body as shown below in table 9 [40].

Miscellaneous research works on ciprofloxacin

Some different results were found during research on CF and its dosage forms by a number of scientists and are discussed below.

Janis Vella et al., conducted studies on “factors affecting the penetration of CF in lower extremity ischemic tissues” indicated the decreased tissue concentrations of CF in patients suffering from more severe forms of the peripheral arterial disease (PAD) [41].

V. V. Sarveshwer Rao et al., conducted studies on “Circadian variation in urinary excretion of CF after a single-dose oral administration at 1000 and 2200 H in Human subjects” and found a significant decrease in the rate and extent of CF excretion during their study [42]. Tomasz Kloskowski et al., proposed that this drug can serve as an adjuvant treatment for lung cancer, due to its capacity of topoisomerase II inhibition [43].

Imran Hayder et al., indicated that TiO₂-based photocatalysis is a feasible way to inactivate the CF drug, as a pretreatment prior to further biological treatments [44]. Gayatri Devi Singh et al., indicated that, with an increase in duration of UV and sunlight treatment duration, the rate of degradation was increased, and led to the gradual inactivation of the antibiotic [45]. Abbas Khan et al., indicated the change of pharmacokinetics of CF when co-administered with diclofenac eye drops [46]. Ron E. Polk et al., resulted in the possibility of renal failure associated with the concomitant administration of cyclosporine and CF [47].

A study on “Comparative Activity of CF, Levofloxacin and Moxifloxacin against Klebsiella pneumoniae, Pseudomonas aeruginosa and Stenotrophomonas maltophilia assessed by minimum inhibitory concentrations and time-kill Studies indicated the activity of CF and levofloxacin antibiotics are equivalent” are [48].

Dannin Ramdhani et al. conducted studies on “Ciprofloxacin resistance among clinical isolates from acute respiratory infections patients at community health centers in taskimlaya, Indonesia” indicated that level of antibiotic (CF) resistance was mediated resistance [49].

CONCLUSION

The present review revealed that analytical methods to determine CF was developed for its pharmacokinetic studies in the first decade of the selected review period (1985-1995). In the second decade, the research work on the physical properties of drug delivery systems of CF was found in the literature. Whereas more research papers were found in the development of novel drug delivery systems of CF in third decade compared to the last 2 decades. The review on CF will be useful for further applications and development of improved drug delivery systems as it helps in the understanding of available applications, drug delivery systems with the already found results/reports on increased bioavailability, prolonged release, gastric retention etc.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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