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Review Article

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 applications and methods development for estimation of CF. It also highlighted the possible interactions and adverse drug reactions of CF and 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

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INTRODUCTION

Ciprofloxacin (CF) is an antibiotic 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 °C [8].

Table 1: Properties of ciprofloxacin

Name of property	Description	Reference number
State	Solid	
Water solubility	1.35 mg/ml	7
Melting point (°C)	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 t_{max} 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, Fe_2SO_4 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 genital 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

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)	69%	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	6-24.80/10 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
Gastro 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*.	15
Controlled release DDS	Films	To treat periodontitis	16
Gastro retentive sustained release DDS	Microbeads	To Prolong duration of action	17
Targeted DDS	Elastic liposomes	To treat acne vulgaris	18
Sustained release DDS	Floating matrix tablets	To extend absorption of CF.	19
Sustained release DDS	Tablets	To prolong the drug release	20
Controlled DDS	Dental films	To treat periodontitis	5
Ophthalmic DDS	Ocular Inserts	To treat ocular conjunctivitis	21
Wound closures	Composite films	For wound healing	22
Floating bioadhesive DDS	Tablets	To increase the stay period of drug in its absorption area and to decrease the dosing interval	23
Swellable and gastro-retentive DDS	Tablets	To prolong gastric emptying time	24
Topical DDS	Films	To treat periodontitis	25
Ophthalmic DDS	Insitu gel	To treat eye infections like dacrocystitis, bacterial conjunctivitis corneal ulceration	26
Multi-unit floating DDS	Beads	To know about the effect of additives	27
Extended-release DDS	Tablets	To Prolong duration of the release	28
The novel vesicular carrier system	Niosomal cream	To improve skin retention and prolong the local effect on skin	29

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

periodontal pathogens, in the form of dental films. Ocular inserts were developed to treat ophthalmic infections. Hence, the list of research work conducted on CF by many researchers is shown in table 5.

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.

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

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 and biological fluids	RP-HPLC	Separation of compounds and to determine the pharmacokinetics of CF	33
Pharmaceutical preparations	HPLC	Quantitative determination of 2nd generation quinolones	34
Ophthalmic solution	UV-Visible spectrophotometry	The first derivative method is successfully applied (difficulty with excipients can overcome by selecting at appropriate wavelength)	35
Pharmaceutical preparations	HPLC with UV detection	Highly efficient for quantification in matrices evaluated	9
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 increased plasma concentrations when co-administered with CF [37]. Hence, CYP1A2 metabolized drugs 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.

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

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 III 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 (NSAIDs)	Increase the risk of central nervous system stimulation and convulsive seizures.	
Oral Anticoagulants	Increase in oral anticoagulant activity	

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

Dosage form	With	Effect	Reference number
Tablet	Food	Delay in the absorption of CF	
Suspension	Food	No delay is observed	39
Any formulation	Dairy products/Calcium-fortified juices	Decrease in the absorption of CF	

Table 9: Adverse drug reactions of ciprofloxacin

Organ/System name	ADR	Reference number
CNS	Nervousness, agitation, insomnia, anxiety, nightmares, dizziness, confusion, tremors, hallucinations, psychotic reaction, depression	38,39,40
CVS	Orthostatic hypotension, Vasculitis	
EYE	Blurred vision, burning, stinging, irritation, itching, tearing, and redness of eyes, eyelid itching, swelling, or crusting, sensitivity to light	
GI System	Nausea, vomiting, diarrhea, constipation, abdominal pain or discomfort, dyspepsia, dysphagia, flatulence, pancreatitis, pseudomembranous colitis	
Urinary system	Albuminuria, candiduria, renal calculi	
Skin	Rashes, exfoliative dermatitis, toxic epidermal necrolysis, erythema, Toxic epidermal necrolysis, Stevens-Johnson syndrome	
Hepatic system	Jaundice, hepatic necrosis	
Musculoskeletal system	Myalgia, myoclonus, tendinitis, tendon rupture	
Others	Phototoxicity	

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 TiO_2-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 *Stenotrophomona maltophilia* assessed by minimum inhibitory concentrations and time-kill Studies indicated the activity of CF and levofloxacin antibiotics are equivalent [48].

Danni ramdhani et. al conducted studies on "Ciprofloxacin resistance among clinical isolates from acute respiratory infections patients at community health centers in tasikmalaya, 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 development 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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