Int. J. Chem. Sci.: 6(4), 2008, 1702-1713

– A REVIEW

NORFLOXACIN : A THERAPEUTIC REVIEW

PRABODH CHANDER SHARMA*, ANKIT SANEJA and SANDEEP JAIN[a]

Institute of Pharmaceutical Sciences, Kurukshetra University,
KURUKSHETRA – 136119 (Haryana) INDIA
[a]Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology,
HISAR – 125001 (Haryana) INDIA

ABSTRACT

This therapeutic review illustrates the chemistry, pharmacology, pharmacokinetics, antibacterial spectrum and interactions of norfloxacin, a fluoroquinolone antibiotic. A special emphasis is laid on the clinical efficacy and antimicrobial spectrum of norfloxacin and its place in clinical therapy. Norfloxacin is generally well tolerated and its adverse effects are not very severe. Regardless of the fact that norfloxacin was introduced long back and many new fluoroquinolones have been introduced thereafter, it still holds a very important place in treatment of several infectious diseases.

Key words : Norfloxacin, Fluoroquinolone, Therapeutic review, Bactericidal, DNA-gyrase

INTRODUCTION

Fluoroquinolones are piperazinyl derivatives of quinolones and are broad spectrum antibiotics widely used for treatment of numerous diseases[1-5]. This relatively new class of antibacterials has received increasing clinical attention and became mainstay in several treatment therapies in recent decades. The infectious disease community has viewed these orally absorbed and synthetically derived agents with special interest, despite the recent development of numerous beta-lactam antibiotics (including penicillins, cephalosporins, carbapenems and monobactams)[6]. Nalidixic acid was the first of a new class of 1, 8-napthyridine antimicrobial agents that have been synthesized in 1962[7]. Since that time, a number of other chemically related compounds have been synthesized, evaluated and introduced in clinical therapy. These newer drugs have a broad antibacterial spectrum that

* Author for correspondence; Mobile: +919416025460 ; E.mail-sharma_prabodh@rediffmail.com; saneja234@gmail.com

includes gentamicin-susceptible and gentamicin-resistant strains of *Pseudomonas aeruginosa,* other multi-resistant, gram-negative rods, gram-positive cocci and beta-lactamase-producing bacteria[6].

Norfloxacin is a widely used representative member of this family and is the first choice of drug for the treatment of bacterial infections of the urinary, biliary, respiratory tracts[8, 9]. It is the first of the fluoroquinolones, to be developed for clinical use[10]. It was patented in 1978 and subsequently became the first fluoroquinolone to receive approval from US Food and Drug Administration (FDA) in 1984[11, 12]. Due to fluorine (F) at the 6th position and piperazine at the 7th position of quinolone carboxylic acid, it has enhanced activity against both; gram positive and gram negative bacteria. Norfloxacin is specifically active against aminoglycoside resistant *Pseudomonas aeruginosa* and betalactamase producing organisms[5]. At this time, a large number of other related compounds including ofloxacin, ciprofloxacin, amifloxacin, enoxacin, pefloxacin, difloxacin, gattifloxacin, sparfloxacin, fleroxacin are in clinical practice and others are in vigorous stages of development and clinical investigation[11].

Chemistry

All clinically important fluoroquinolones are synthetically derived from nalidixic acid i. e. 1, 8- naphthyridine (Fig. 1)[12]. Chemically, norfloxacin (Fig. 2) is, 1-ethyl-6-fluoro 1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid[13].

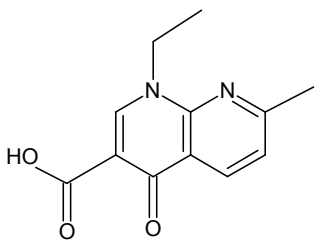

Fig. 1. Nalidixic Acid

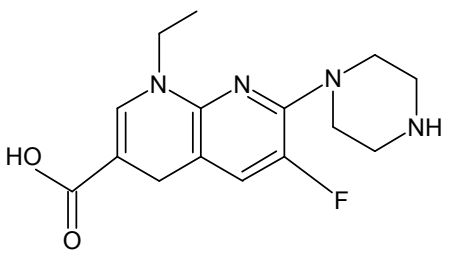

Fig. 2. Norfloxacin

Its empirical formula is $C_{16}H_{18}FN_3O_3$ and physically, it is a white to pale yellow crystalline powder having molecular mass 319.331 g/mol and melting point of about 221^0C. It is odorless and has a bitter taste. It is freely soluble in glacial acetic acid and very slightly soluble in ethanol, methanol and water[14, 15]. Its octanol-water partition coefficient is 0.46[15].

Pharmacology

Mechanism of action

The fluoroquinolone antibacterials in general and norfloxacin in particular are bactericidal in their action[6]. Carboxylic acid group and the ketone group are responsible for the antibacterial activity, whereas substituents in positions 1 and 7 decide effectiveness and potency of the fluoroquinolone[1, 16]. Norfloxacin inhibits bacterial deoxyribose nucleic acid (DNA) gyrase (topoisomerase II), an enzyme, which converts covalently closed circular DNA into negative supercoils[15, 17-19]. This DNA gyrase, present in bacteria is the only topoisomerase (topoisomerase–II) known, which is able to introduce negative superhelical turns into duplex DNA. The introduction of supercoils into DNA is an energy demanding process. This DNA gyrase enzyme is able to couple the energy released from the hydrolysis of ATP to drive the formation of supercoils. Gyrase can also remove positive supercoils in the presence of ATP and relax negatively (but not positively) supercoiled DNA in the absence of ATP[17]. It is believed that the drug directly acts on DNA, producing a covalent attachment of DNA gyrase to DNA, which forms a complex that is inaccessible to the action of DNA polymerase; thus, leading to prevention of DNA synthesis and replication which ultimately results in rapid cell death[15, 20]. Thus, this unique mechanism of action accounts for the low rate of cross-resistance with other antimicrobial classes[12]. Quinolones similarly inhibit the *in vitro* activities of DNA topoisomerase IV by interfering with separation of replicated chromosomal DNA into respective daughter cells during cell division. This action is believed to be the primary target in gram-positive bacteria. At the molecular level, three specific events are attributed to norfloxacin[12, 21, 22] :

(i) Inhibition of ATP – dependent DNA supercoiling reaction catalyzed by DNA gyrase,

(ii) Inhibition of relaxation of supercoiled DNA, and

(iii) Promotion of the double – strand DNA breakage.

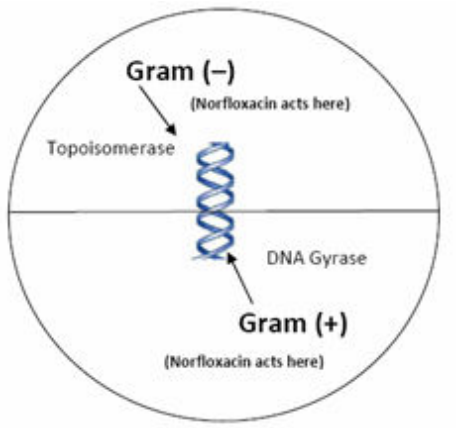

Fig. 3: Mechanism of action of norfloxacin

Toxicology

Available studies provide information on adverse effects of norfloxacin and ecoxacin, each delivered at doses of 400 mg twice daily for 3 to 14 days. In each comparative study, the adverse effects reported with norfloxacin were similar to[23-32] or significantly less frequent[31] than those reported with the comparison drugs like trimethoprim, sulfamethoxazole, amoxicillin, or nalidixic acid. Norfloxacin was generally well tolerated with adverse reactions (including both possible and probable reactions, not all necessarily drug related) reported in less than 10% of patients in most of the studies (range, 0 to 26%) for a total of 77 adverse reactions among 1, 136 patients treated (6.8%) in the 12 studies of urinary tract infections[23-33, 34]. Gastrointestinal symptoms (nausea, vomiting, anorexia) and central nervous system symptoms (lightheadedness, headache, drowsiness, insomnia) were the most frequently reported but they were not found to be so severe that required cessation of therapy. In four patients with joint swelling or tendonitis (three involving fingers)[23, 33-35], two of whom had recurrences upon rechallenge with norfloxacin, either a low frequency (1.6%)[31] or no abnormalities of laboratory tests (blood counts and liver function tests)[25, 27, 29, 33, 34, 36] were reported. In one study equivalent higher frequencies of laboratory abnormalities were found both in patients receiving norfloxacin and in those receiving trimethoprim-sulfamethoxazole[26].

Adverse effects

The most common adverse effects associated with the fluoroquinolones are gastro intestinal (GI) effects such as nausea, vomiting and diarrhoea reported in about 1% - 5% patients[12, 37, 38], skin disturbances (< 2.5%)[37] and CNS effects, including headaches and

dizziness (~ 1% - 2%)[37,39]. Less common adverse effects are sleep disturbances, hallucinations, depressions and seizures[37]. These adverse effects are generally mild and self limiting and seldom result in withdrawal of treatment[40]. Incidences of most common adverse effects of norfloxacin and other common agents are tabulated in Table 1.

Table 1. Incidences of the most common drug related adverse events occurring with the common fluoroquinolones (based on package inserts)[12]

Event (%)	Ciprofloxacin	Levofloxacin	Sparfloxacin	Trovafloxacin	Lomefloxacin	Norfloxacin
Nausea	5.2	1.2	4.3	8	3.7	2.6 - 4.2
Diarrhoea	2.3	1.2	4.6	2	1.4	0.3 – 1.0
Taste Perversion	0.02	0.2	1.4	-	< 1.0	-
Headache	1.2	0.1	4.2	5	3.2	2.8
Dizziness	< 1.0	0.3	2.0	11	2.3	1.7
Phototoxicity	0.4	< 0.1	7.9	< 0.03	2.4	1.6

Pharmacokinetics

For norfloxacin, after an oral dose of 200-400 mg, mean peak serum concentrations of 0.8 ± 0.3 and 1.5 ± 0.6 mg L^{-1}, respectively are achieved within 60 -90 minutes. The presence of food/dairy products slightly impairs its absorption. Studies in animals show that the volume of distribution of norfloxacin is very large, about 50% of the body weight and the bioavailability is 50 – 80%. Approximately 15% of the drug in the serum is bound to plasma proteins. Following oral administration of 200 mg, the concentration in tonsillar tissue, maxillary sinus mucosa, vaginal tissue, cervical tissue, saplings, ovaries, renal cortex and the gallbladder wall were only slightly lower than the serum concentrations. Bile, liver and renal medulla had drug concentrations higher than the serum. Norfloxacin has not been found in human milk after a single oral dose of 200 mg. Norfloxacin has a very low CNS penetration due to relatively low lipophilicity[41]. Norfloxacin is cleared from the body through the kidneys, biliary excretion and metabolism. Its elimination half life is 3 h approximately[17]. A steady state concentration of norfloxacin is generally attained within two days of dosing. Pharmacokinetic properties and distribution of norfloxacin in

body are summarized in Table 2 and 3.

Table 2. Pharmacokinetic properties of norfloxacin[22]

Drug	Half life (h)	Oral bioavailability (%)	Peak serum concentrations (µg/mL)	Oral dose (mg)	Primary route of excretion
Norfloxacin	3.5 – 5	80	1.5	400	Renal

Table 3. Pharmacological distribution of norfloxacin in humans[23]

Drug	Dose (mg)	Route[a]	Serum			Urine			Blister fluid	
			C_{max}[b] (µg/mL)	$t_{½}$[c] (h)	AUC[d] (µg. h/mL)	C_{max} (µg/mL)	Recovery (%)	V_d[e] (Litres)	C_{max} (µg/mL)	% of serum
Norfloxacin	400	p. o.	1.5	3-4	5-6	98-114	28	NA[f]	1.0	67

[a] p. o. Perorally : i. v. intravenously, [b] Maximum concentration in designated fluid, [c] Terminal half life of elimination from serum, [d] Area under the curve of a plot of serum concentration versus time, [e] volume of distribution, [f] NA, Data not available

Metabolism

Elimination of norfloxacin is partly by hepatic metabolism by P450 enzymes and partly by renal excretion[42, 43]. Quinolones get conjugated with glucuronic acid at the COOH group at 3-position. The major metabolites are derived from chemical substitutions on the piperazine ring. These occur by modification of the amino nitrogen with formation of formyl and acetyl derivatives or by oxidation of a carbon atom in the piperazine ring to a keto group designated as the oxo derivative[15]. For norfloxacin, enoxacin and ciprofloxacin, metabolites constituted about 15-30% of the drug, recoverable in urine[23].

Antimicrobial spectrum

Norfloxacin in general is more active, with a broader spectrum of inhibition, than earlier quinolones. The antimicrobial activity *in vitro* is diminished by acidic pH and high

concentrations of Mg^{2+} ions in the medium. It is active against both; gram positive and gram negative bacterials[15, 43]. The fluorine atom at the 6th position increases potency against gram negative organisms and the piperazine moiety at the 7th position is responsible for anti-pseudomonal activity. More than 90% of strains (MIC_{90}) among the species of Enterobaciteriaceae are inhibited at concentrations lower than 2 mg L^{-1}. The exceptions are *Serratia marcescens* and *Providencia stuartii*, which are more resistant with an MIC_{90} of 3.1 mg L^{-1}. Pathogenic enteric bacteria, including *Salmonella spp., Shigella spp., Yersinia enterocolitica, Aeromonas hydrophila, Plesiomonas shigelloides, Vibrio parahaemolyticus, Vibrio cholera and campylobacter jejunii* are very susceptible with an MIC_{90} of < 1 mg L^{-1}. Norfloxacin is active against *Neisseria meningitidis, Branhamella catarrhalis and N. gonorrhea* including β-lactamase producing strains at lower concentrations (MIC_{90} < 0.06 mg L^{-1})[4, 43, 44].

The MIC_{90} for *Pseudomonas aeruginosa* ranges from 1 to 3.1 mg L^{-1}, while others, i.e. *Pseudomonas spp. and Acinetobacter spp.* are more resistant. The activity against *Streptococci*, including methicillin resistant strains, is lower than the activity against Gram negative bacteria. The range of MIC_{90} is from 1 to 6.1 mg L^{-1}. Activity against streptococci is even less and more variable than against staphylococci with an MIC_{90} of 0.5 – 32 mg L^{-1}. Norfloxacin is generally inactive against most clinically important anaerobic bacteria like mycobacteria, *Mycoplasma, Chlamydia and Ureaplasma*. Synergy between norfloxacin and amphotericin B has been reported for *Candida* spp. and *Cryptococcus* spp. No plasmid mediated norfloxacin resistance has been reported[15, 45-49].

Norfloxacin, when given with one exception[24] in doses of 400 mg orally twice daily, demonstrated significantly higher[30, 31] or equivalent rates of cure, when compared in eight randomized, nonblinded studies to orally administered trimethoprim-sulfamethoxazole [24-27, 31, 32], amoxicillin[28], or nalidixic acid[30]. When specified (eight studies), most studies included only patients with uncomplicated infections (absence of catheters, structural defects in the urinary tract, or abnormal renal function)[24, 25, 27, 29-31, 35, 37]. In the two studies that included complicated infections (catheterized patients, some elderly with mild degrees of azotemia), 84 to 95% of the patients reported were cured[28, 36]. In one comparative study, norfloxacin cured 19 of 20 patients (95%) and amoxicillin cured 15 of 20 patients (75%) ($p = 0.08$, Fisher's exact test)[29]. In three other studies[26, 29, 31], a small number of patients with antibody-coated bacteria in the urine, suggesting pyelonephritis, were also cured. In most instances, the infecting organisms were *Escherichia coli* or other enteric gram- negative bacilli, but lesser numbers of urinary tract infections caused by *Pseudomonas aeruginosa* were also successfully treated [27, 29, 36].

Resistance

The most important acquired quinolone resistance arises from mutation of bacterial DNA gyrase enzyme. This phenomenon has been elucidated in a number of bacterial species as involving the change of a single nucleotide in the gyrase gene. Resistance to norfloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range : 10^{-9} to 10^{-12} cells). Resistant organisms have emerged during therapy with norfloxacin in less than 1% of patients treated. Organisms in which development of resistance is greatest are *Psedudomonas aeruginosa, Klebsiella pneumonia, Acinetobacter spp. and Enterococcus spp.* There is generally no cross resistance between norfloxacin and other classes of antibacterial agents. Therefore, norfloxacin may demonstrate activity against indicated organisms resistant to some other antimicrobial agents including the aminoglycosides, penicillins, cephalosporins, tetracyclines, macrolides and sulfonamides, including combinations of sulfamethoxazole and trimethoprim. Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin[17, 50].

During fluoroquinolone therapy, resistant organisms emerge with a frequency of about one in 10^7-10^9, especially among *Staphylococci*, *pseudomonas* and *serratia*. Resistance is due to one or more point mutations in the quinolone binding region of the target enzymes or to a change in the permeability of the organism. A subunit of gyrase, topoisomerase IV is a secondary target in *E. coli* that is altered in mutants expressing higher levels of resistance. In *staphylococci* and *streptococci* the situation is reversed : topoisomerase IV is usually the primary target and gyrase is the secondary target. Resistance to one fluoroquinolone, particularly if of high level, generally confers cross resistance to all other members of this class. With the increasing use of fluoroquinolones for a variety of infections, including respiratory tract infections, fluoroquinolone resistance has emerged among strains of *Streptococcus pneumoniae*[22].

Interactions

All fluoroquinolone agents interact with multivalent cation containing products, such as aluminium or magnesium containing antacids and the product containing antacids and calcium, iron or zinc[15, 17, 22, 41-43]. Co-administration of norfloxacin with antacids decreases the absorption of norfloxacin from the gastrointestinal tract, which might be hazardous during the treatment of a serious infection. Simultaneous administration of other quinolones with theophylline interferes with theophylline disposition resulting in high theophylline levels. Close monitoring of theophylline levels is recommended, when theophylline and norfloxacin are co-administered. Elevated serum levels of cyclosporine

have been reported with concomitant use of norfloxacin. Probenecid reduces the urinary excretion by inhibiting tubular secretion. Drugs which cause the urine to become alkaline, such as sodium bicarbonate, carbonic anhydrase inhibitors and citrates, reduce the solubility of norfloxacin and may increase the possibility of crystalluria[15].

Clinical applications/ therapeutic uses

Norfloxacin has been effective in the treatment of urinary tract infections, *Neisseria gonorrhoea* urethritis and/or cervicitis. Norfloxacin (400 mg twice or three times daily for 5 days) was as effective as co –trimoxazole or nalidixic acid in the treatment of bacterial gastroenteritis caused by enterotoxigenic *E. coli* or *Shigella species*. Effectiveness of norfloxacin oral dosage has been evidenced in treatment of typhoid fever (400 mg three daily for 14 days)[15, 51]. Oral non-absorbable antibiotics co-trimoxazole and most recent quinolones, have been used to reduce the incidence of Gram-negative infection in certain groups of high risk patients. Norfloxacin, ofloxacin and ciprofloxacin have shown to reduce infection rates, although resistant bacteria may emerge during therapy. Norfloxacin has been used with considerable success to reduce the rate of bacterial peritonitis in patients with hepatic cirrhosis and ascites[52]. It may be used in the treatment of lower respiratory tract infections caused by susceptible bacteria. Norfloxacin ophthalmic solution was as effective as chloramphenicol in the treatment of bacterial conjunctivitis[53].

Although the fluoroquinolones are presently used to treat tuberculosis primarily in cases involving resistance or intolerance to first line antituberculosis therapy, these drugs are potential first line agents and are under study for this indication. However, there is concern about the development of fluoroquinolone resistance in *Mycobacterium tuberculosis*, particularly when administrated as a monotherapy or as the only active agent in a failing multidrug regimen [54].

REFERENCES

1. E. Turiel, A. Mart´in-Esteban and J. L. Tadeo, J. Chromat. A, **1172**, 97 (2007).
2. Ch. G. Daughton and T. A. Ternes, Environ. Health Perspect, **107**, 907 (1999).
3. W. Gau, J. Kurz, U. Petersen, H. Ploschke and C. Wuensche, Drug Res., **36**, 1545 (1986).
4. A. R. Shaikh, R. Giridhar and M. R. Yadav, Int. J. Pharm., **332**, 24 (2007).
5. P. Naumann and C. Dopp., Internist (Berl.), **30**, 20 (1989).
6. E. J. C. Goldstein, Am. J. Med., **82**, 3 (1987).

7. G. Y. Lesher, E. J. Froelich and M. D. Grutt, J. Med. Pharm. Chem., **5**, 1063 (1962).

8. M. Co´Rdoba-Dı´Az, M. Co´Rdoba-Borrego and D. Co´Rdoba-Dı´Az, J. Pharm. Biom. Anal., **18**, 865 (1998).

9. P. N. Bennet and M. J. Brown, Clinical Pharmacology, Vol. IX Elsevier, New Delhi, (2005) p. 132.

10. R. C. Moellering, Am. J. Med., **82**, 1 (1987).

11. P. C. Appelbaum and P. A. Hunter, Int. J. Antimicrob. Agents, **16**, 5 (2000).

12. J. Bertino and D. Fish, Clinic. Therap., **22**, 798 (2000).

13. M. S. Refat, Spect. Acta Part A, **68**, 1393 (2007).

14. M. Cordoba-Boreggo, M. Cordoba-Diaz, I. Bernabe and D. Cordoba-Diaz, J. Pharm. Biomed. Anal., **41**, 977 (1996).

15. A. Boobis, M. Rawlins, S. Thomas and M. Wikins, Therapeutic Drugs**,** Vol. 2, Churchill Living Stone, (1999) p. 137.

16. B. Suh and B. Lorber, Med. Clin. N. Am., **79**, 869 (1995).

17. S. L. Dax, Antibacterial Chemotherapeutic Agents, Blackie Academic and Professional, Newyork, (1997) p. 298.

18. M. Takhata and T. Nishino, Antimicrob. Agents Chemother., **32**, 1192 (1988).

19. L. L. Shen, J. Biol. Chem., **264**, 2973 (1989).

20. E. C. Engle, S. H. Manes and K. Drilica, J. Bacteriol., **149**, 92 (1983).

21. J. M. Blondeau, Clin. Ther., **21,** 3 (1999).

22. B. G. Katzung, Basic and Clinical Pharamacology, Mcgraw Hill (Tx), Vol. IX**,** **(**2004), p. 777.

23. D. C. Hooper and J. S. Wolfson, Antimicrob. Agents Chemother., **28,** 716 (1985).

24. H. Giamarellou, J. Tsaragarahis, G. Petrikkos and G. K. Daikos, Eur. J. Clin. Microbiol., **2,** 266 (1983).

25. E. J. C. Goldstein, M. L. Alpert and B. P. Ginsberg, Antimicrob. Agents Chemother., **27**, 741 (1984).

26. J. G. Guerra, E. Falconi, J. C. Palomino, L. Benavente and E. A. Mayolo, Eur. J. Clin. Microbiol., **2**, 260 (1983).

27. D. A. Haase, G. K. M. Harding, M. J. Thomson, J. K. Kennedy, B. A. Urias and A. R. Ronald, Antimicrob. Agents and Chemother. ¸ **26**, 481 (1984).

28. D. A. Leigh, E. C. Smith and J. Marriner, J. Antimicrob. Chemother., **13**, 79 (1984).

29. G. Panichi, A. Pantosi and G. P. Testore, J. Antimicrob. Chemother., **11**, 589 (1983).

30. D. S. Reeves, R. W. Lacey, R. W. Mummery, M. Mahendra, A. J. Bint and S. W. B. Newson, J. Antimicrob. Chemother., **13** (**Suppl. B),** 99 (1984).

31. J. Sabbaj, V. L. Hoagland and W. J. Shih, Antimicrob. Agents Chemother., **27**, 297 (1985).

32. B. Watt, I. Chait, M. C. Kelsey, S. W. B. Newsom, R. A. Newsom, J. Smith, P. D. Toase, N. B. Deaney, E. M. Round, R. Vogel and W. J. C. Currrie, J. Antimicrob. Chemother., **13 (Suppl. B),** 89 (1984).

33. N. B. Deany, R. Vogel, M. J. Vandenburg and W. J. C. Currie, Practitioner, **228**, 111 (1984).

34. C. P. Kirby, J. Antimicrob. Chemother., **13 (Suppl. B),** 107 (1984).

35. R. R. Bailey, J. A. Kirk and B. A. Peddie, N. Z. Med. J., **96**, 590 (1983).

36. D. A. Leigh and F. X. S. Emmanuel, J. Antimicrob. Chemother., **13 (Suppl. B),** 85 (1984).

37. P. Ball and G. Tillotson, Drug Saf., **13**, 343 (1995).

38. J. S. Wolfson and D. C. Hooper, Am. J. Med., **91**, 153s (1991).

39. R. Jaknegt, Pharm. Weekbl. Sci., **11**, 124 (1989).

40. P. Ball, Clin. Invest. Med., **12**, 28 (1989).

41. A. Delon, F. O. Huguet, P. Courtois, J. M. Vierfond, S. B. Bouquet and W. Couet, J. Pharmaco. Experi. Therap., **280**, 983, (1997).

42. H. P. Rang, M. M. Dale, J. M. Ritter and P. K. Moore, Pharmacology, Fifth Edition, Elsevier, Churchill Livingstone, Edinburg (2003) p. 647.

43. E. K. Efthimiadou, G. Psomas, Y. Sanakis, N. Katsaros and A. Karaliota, Spectro. Acta Part_A, XXX, (2007) XXXX.

44. E. K. Efthimiadou, G. Psomas, Y. Sanakis, N. Katsaros and A. Karaliota, J. Inorg. Biochem., **101**, 525 (2007).

45. A. Ito, K. Hirai and M. Inone, Antimicrob. Agents Chemother., **17**, 103 (1980).

46. A. King, C. Warren, K. Shannon and J. Philips, Antimicrob. Agents Chemother., **21**, 607 (1982).

47. S. R. Norrby and M. Jonsson, Antibacter. Chemother., **23**, 15 (1983).

48. H. C. Neu and P. Labthavikul, Antimicrob. Agents Chemother., **22**, 23 (1982).

49. S. Mitsuhashi, Revi. Infec. Dis., **10** (**Suppl. 1),** S 27 (1988).

50. S. B. Bari, B. M. Mahajan and S. J. Surana, Ind. J. Pharm. Educ. Res., **42 (1),** 3 (2008).

51. S. K. Bhattacharya, M. K. Bhattacharya and P. Dutta, Antimicrob. Agents Chemother., **34**, 939 (1990).

52. P. Gines, A. Rimola and R. Planas, Hepatoplogy, **12**, 716 (1990).

53. I. M. Miller, J. M. Wittereich, T. Cook and R. Vogel, Eye, **6**, 111 (1992).

54. A. S. Ginsburg, J. H. Grosset and W. R. Bishai, Lanc. Infec. Dis., **3**, 432 (2003).

Accepted : 16.07.2008