

Revised Abstract

Background: Finafloxacin is a novel member of the fluoroquinolone class of antibiotics. Specifically, finafloxacin belongs to a new 8-cyano subclass. The agent contains a novel base component which confers improved antibacterial activity under acidic conditions, where the activity of many existing fluoroquinolones is impaired. The current report describes the broad-spectrum of activity of this agent. **Methods:** A total of 985 isolates were tested and comprised of 410 gram-positive and 575 gram-negative clinical isolates from 2009-2010. MICs were determined according to CLSI M07-A8 broth microdilution methodology. **Results:** Activity of finafloxacin against the study isolates is shown below in the Table.

Species (n)	Median MIC	MIC ₉₀	Species (n)	Median MIC	MIC ₉₀
<i>E. faecalis</i> (25)	2	>32	<i>A. baumannii</i> (25)	8	>32
<i>E. faecium</i> (25)	>32	>32	<i>C. freundii</i> (24)	0.25	>32
<i>S. aureus</i> (101)	0.12	8	<i>E. coli</i> (99)	0.12	>32
MSSA (76)	0.12	0.12	<i>H. influenzae</i> (100)	0.008	0.03
MRSA (25)	4	>32	<i>K. pneumoniae</i> (102)	0.25	>32
<i>S. epidermidis</i> (100)	0.12	>32	<i>M. catarrhalis</i> (26)	0.03	0.03
MSSE (50)	0.12	0.25	<i>M. organii</i> (25)	1	>32
MRSE (50)	4	>32	<i>P. mirabilis</i> (25)	1	>32
<i>S. agalactiae</i> (24)	0.5	1	<i>Providencia</i> spp. (24)	4	>32
<i>S. pneumoniae</i> (100)	1	1	<i>P. aeruginosa</i> (100)	4	>32
<i>S. pyogenes</i> (100)	0.5	1	<i>S. marcescens</i> (25)	2	8
Viridans streptococci (25)	1	4			

Values shown are MICs expressed in mcg/ml.

Conclusions: By analysis of all median MIC values, the spectrum of *in vitro* activity of finafloxacin included all species tested, with the exception of *E. faecium* for which the median MIC was >32 mcg/ml. By MIC₉₀, finafloxacin was most active against *H. influenzae* and *M. catarrhalis* (MIC₉₀ 0.03 mcg/ml) and streptococci (MIC₉₀ range 1 – 4 mcg/ml). As expected with all fluoroquinolones, activity against methicillin-resistant staphylococci was limited.

Introduction

Finafloxacin is a novel member of the fluoroquinolone class of antibiotics. Specifically, finafloxacin belongs to a new 8-cyano subclass. The agent contains a novel base component which confers improved antibacterial activity under acidic conditions, where the activity of many existing fluoroquinolones is impaired. Finafloxacin is currently in clinical development with MerLion Pharmaceuticals. Under license with Alcon Pharmaceuticals, USA, finafloxacin is being developed for treating ear infections, including acute otitis externa and acute otitis media. In addition to otic and ophthalmic indications, finafloxacin, which has already shown potential for the treatment of a range of infections in Phase IIa clinical studies, is also being evaluated in critical care and hospital based infection settings.

In order to more thoroughly investigate the spectrum of activity of finafloxacin, a total of 985 aerobic gram-positive and gram-negative clinical isolates were tested for susceptibility to finafloxacin and comparator agents.

Materials & Methods

Antimicrobial Susceptibility Testing

Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (Clinical and Laboratory Standards Institute (CLSI), *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard- Eighth Edition*, M07-A8, Wayne, PA, USA, 2009). All panels were produced at IHMA.

Cation-adjusted Mueller-Hinton broth (CAMHB), cation-adjusted Mueller-Hinton broth supplemented with 3% laked horse blood (MHB/LHB) and *Haemophilus* Test Medium broth (HTM) were used as the test media. Endpoints were determined following CLSI guidelines (CLSI, *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement* M100-S21, Wayne, PA, USA, 2011).

As finafloxacin is known to possess improved activity at acidic pH, unlike other fluoroquinolones, susceptibility tests were performed at standard pH (pH 7.2) and acidic pH (pH 5.8).

Quality control (QC)

QC testing was performed each day of testing as specified by CLSI using *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247.

Data Handling and Analysis

The mean MIC (arithmetic), median (mcg/ml), and MIC₉₀ (mcg/ml) were determined for all antimicrobial agents tested.

Results

Table 1. Comparison of finafloxacin MIC₉₀s and median MICs against gram-positive bacteria.

	MIC ₉₀ (mcg/ml)			
	<i>E. faecalis</i> (25)	<i>E. faecium</i> (25)	<i>S. aureus</i> (101)	<i>S. epidermidis</i> (100)
pH 7.2	>32	>32	8	>32
pH 5.8	32	>32	4	16
	Median MIC(mcg/ml)			
	<i>E. faecalis</i> (25)	<i>E. faecium</i> (25)	<i>S. aureus</i> (101)	<i>S. epidermidis</i> (100)
pH 7.2	2	>32	0.12	0.12
pH 5.8	1	32	0.06	0.06
	MIC ₉₀ (mcg/ml)			
	<i>S. agalactiae</i> (24)	<i>S. pneumoniae</i> (100)	<i>S. pyogenes</i> (100)	Viridans group streptococci (25)
pH 7.2	1	1	1	4
pH 5.8	0.25	0.5	0.25	1

Table 2. Comparison of finafloxacin MIC₉₀s and median MICs against gram-negative bacteria.

	MIC ₉₀ (mcg/ml)					
	<i>A. baumannii</i> (25)	<i>C. freundii</i> (24)	<i>E. coli</i> (99)	<i>H. influenzae</i> (100)	<i>K. pneumoniae</i> (102)	<i>M. catarrhalis</i> (26)
pH 7.2	>32	>32	>32	0.03	>32	0.03
pH 5.8	32	8	16	0.008	16	≤0.015
	Median (mcg/ml)					
	<i>A. baumannii</i> (25)	<i>C. freundii</i> (24)	<i>E. coli</i> (99)	<i>H. influenzae</i> (100)	<i>K. pneumoniae</i> (102)	<i>M. catarrhalis</i> (26)
pH 7.2	8	0.25	0.12	0.008	0.25	0.03
pH 5.8	1	0.06	0.03	≤0.004	0.06	≤0.015
	Median (mcg/ml)					
	<i>M. organii</i> (25)	<i>P. mirabilis</i> (25)	<i>Providencia</i> spp. (24)	<i>P. aeruginosa</i> (100)	<i>S. marcescens</i> (25)	
pH 7.2	1	1	4	4	2	
pH 5.8	0.25	0.25	0.5	0.5	0.5	

Figure 1. Activity of finafloxacin and moxifloxacin against streptococci: MIC₉₀ at standard pH (7.2) and acidic pH (5.8).

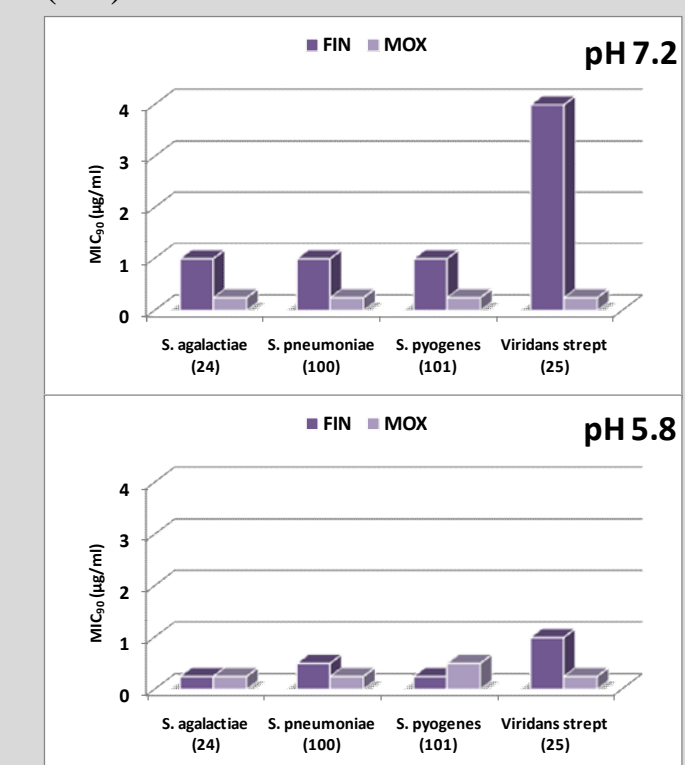


Figure 2. Activity of finafloxacin and moxifloxacin against streptococci: Mean MIC at standard pH (7.2) and acidic pH (5.8).

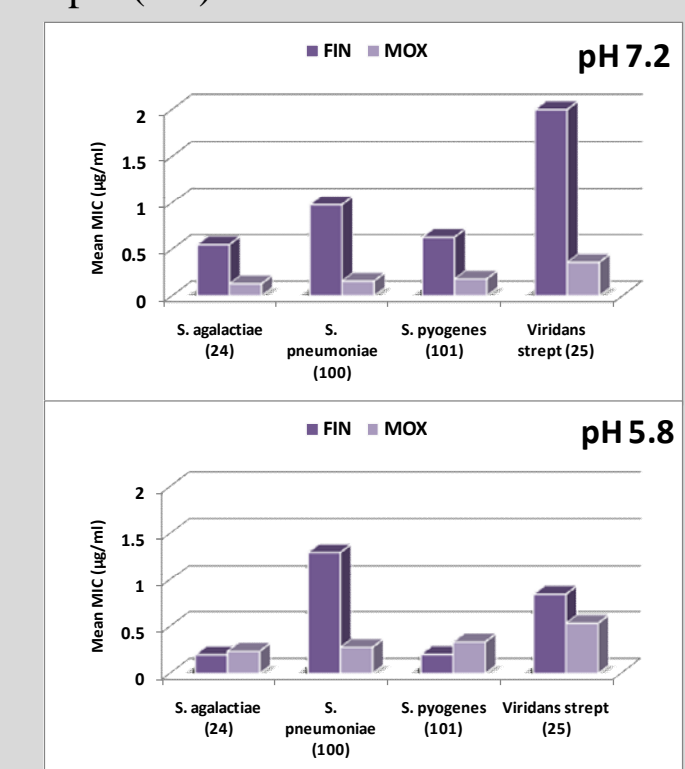


Figure 3. Activity of finafloxacin and moxifloxacin against *H. influenzae* and *M. catarrhalis*: MIC₉₀ at standard pH (7.2) and acidic pH (5.8).

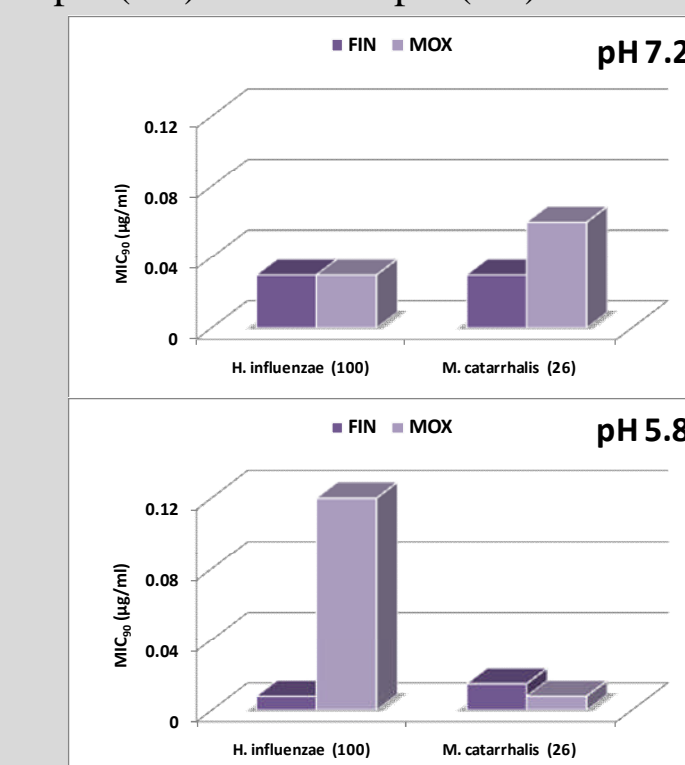
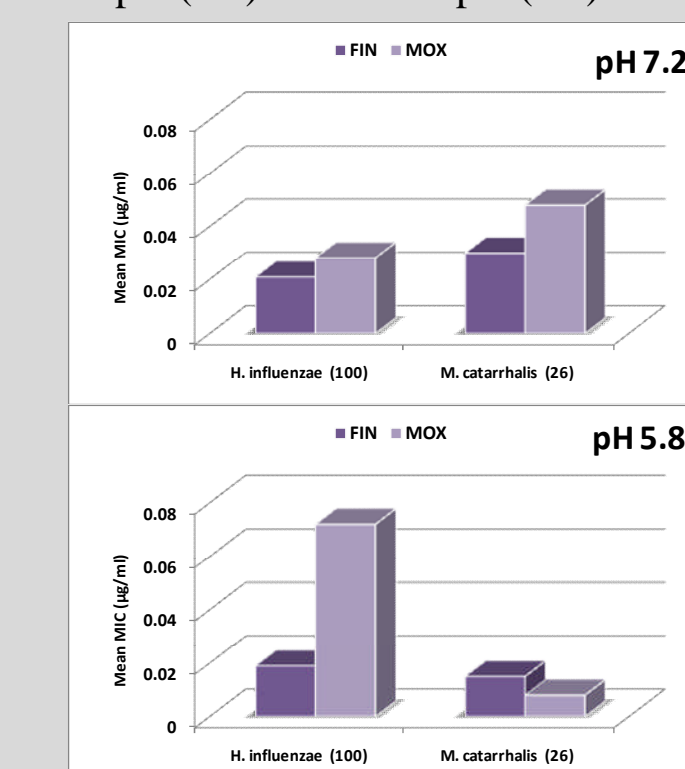


Figure 4. Activity of finafloxacin and moxifloxacin against *H. influenzae* and *M. catarrhalis*: Mean MIC at standard pH (7.2) and acidic pH (5.8).



Conclusions

- Finafloxacin was active against all gram-positive and gram-negative species in the current study and was generally more active under acidic conditions as compared with standard pH (pH 7.2).
- Against gram-positive organisms, finafloxacin was most active against the streptococci with MIC₉₀s ranging from 1 – 4 mcg/ml (standard pH) to 0.25 – 1 mcg/ml (pH 5.8). Activity against staphylococci was generally limited. Certain *E. faecium* strains were susceptible to FIN (Min MIC = 0.5 at pH 5.8), however the majority of strains in this study demonstrated poor susceptibility (Median MIC = 32 at pH 5.8). Against gram-negative organisms, finafloxacin was most active against *H. influenzae* and *M. catarrhalis* with MIC₉₀s for both of 0.03 mcg/ml at standard pH and MIC₉₀s one to two dilutions lower at pH 5.8. Activity against *Enterobacteriaceae* and non-fermenters was limited.
- Finafloxacin is currently under clinical development for the treatment of systemic infections and local infections for which pharmacokinetic / pharmacodynamic data will help to establish the optimal target pathogens per each clinical indication.