CHAPTER 4

Gemifloxacin

Badraddin M.H. Al-Hadiya[*] and
Ashraf M.M. Mahmoud[†]

Contents

[*] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia

[†] Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia

---

Profiles of Drug Substances, Excipients, and Related Methodology, Volume 36
ISSN 1871-5125, DOI: 10.1016/B978-0-12-387667-6.00004-X

1. INTRODUCTION

Gemifloxacin is a fourth generation synthetic broad-spectrum fluorinated quinolone antibacterial agent for oral administration (http://en.wikipedia.org/wiki/Gemifloxacin_mesylate). It is discovered by Hong *et al.* [1] since 1997, and is present in two forms; either as free gemifloxacin base or as gemifloxacin mesylate salt. Gemifloxacin has a broad-spectrum activity against both Gram-negative and Gram-positive microorganisms [2–5]. The new oxime-pyrrolidine derivative moiety of gemifloxacin is the responsible moiety for its new unique activity as compared to the reported fluoroquinolnes.

2. DESCRIPTION [6]

2.1. Nomenclature

2.1.1. CAS name

7-[3-(Aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid

2.1.2. IUPAC name

7-[(4Z)-3-(Aminomethyl)-4-methoxyimino-pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,8-naphthyridine-3-carboxylic acid

2.1.3. Proprietary names

Factive® (tablets were formulated by Oscient Pharmaceuticals, USA)

2.1.4. Nonproprietary names

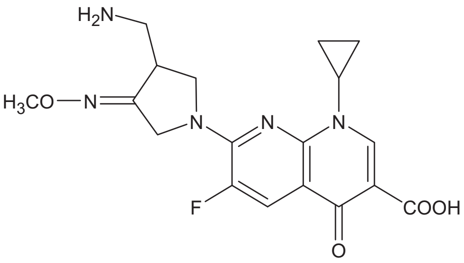
Gemifloxacin
LB20304
SB-265805

2.2. Formulae

2.2.1. Empirical

Gemifloxacin	$C_{18}H_{20}FN_5O_4$
Gemifloxacin mesylate	$C_{18}H_{20}FN_5O_4 \cdot CH_4O_3S$

2.2.2. Structural



2.2.3. CAS Registery Number

175463-14-6 is the CAS Registry Number of gemifloxacin

2.3. Molecular weight

Gemifloxacin has molecular weight of 389.38, whereas gemifloxacin mesylate has molecular weight of 485.49.

2.4. Elemental composition for gemifloxacin

C: 55.52%
H: 5.18%
F: 4.88%
N: 17.99%
O: 16.44%

2.5. Appearance, color, and odor

Gemifloxacin is off-white, amorphous solid from chloroform–ethanol. It has only a slight characteristic odor. However, the mesylate salt is a white to light brown solid.

3. PHYSICAL CHARACTERISTICS

3.1. Melting behavior

The melting point range of gemifloxacin mesylate is 235–237 °C.

3.2. Solubility

Gemifloxacin mesylate is freely soluble in water at neutral, pH 7.0. Its water solubility has been reported (http://www.rxlist.com/factive-drug.htm) as 350 mg/ml at 25 °C. It is soluble in methanol, 0.1 N hydrochloric acid and 0.1 N sodium hydroxide solutions.

3.3. Hydrophobicity

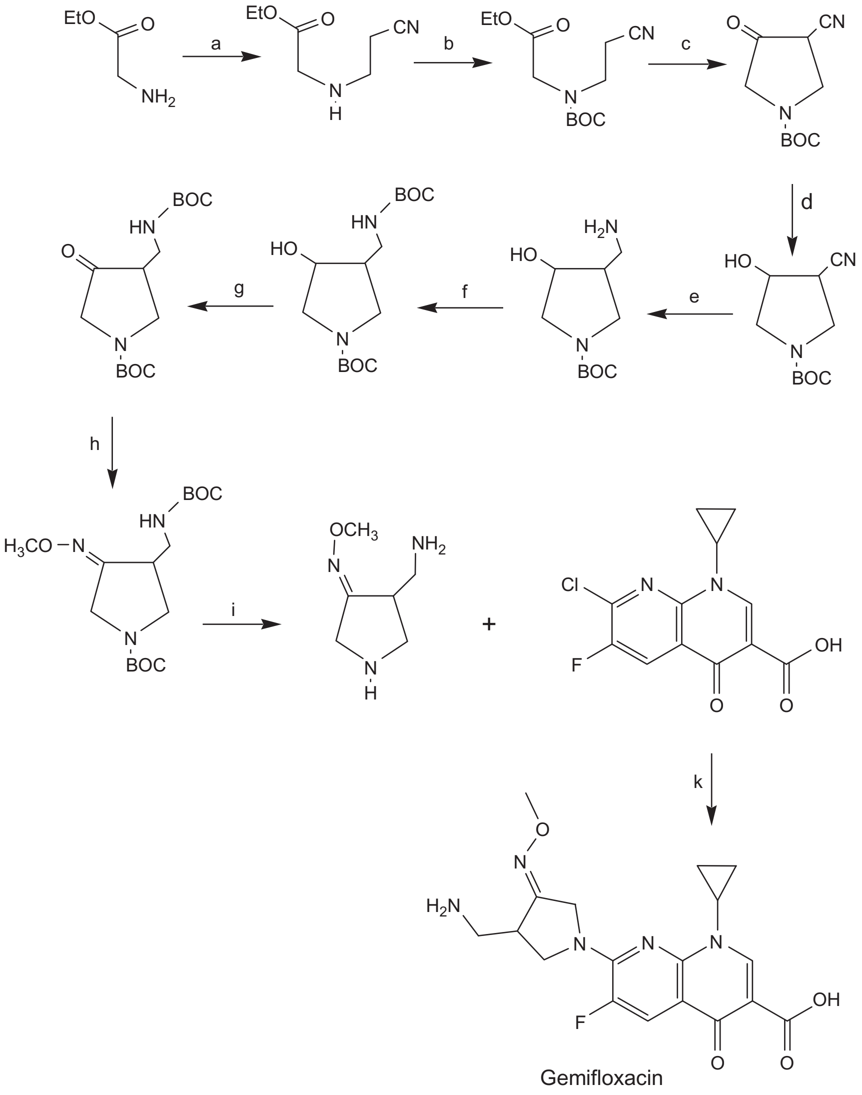
The Experimental Log P/Hydrophobicity of gemifloxacin mesylate is 2.3.

4. SYNTHESIS [2]

The design and synthesis of the new oxime-functionalized pyrrolidine derivative of gemifloxacin, which bear an alkyloxime substituent in the 4-position and an aminomethyl substituent in the 3-position of the pyrrolidine ring, was first described in Scheme 4.1 starting from step (a) to step (i) in the scheme. Then, the new pyrrolidine derivative moiety was coupled with a certain quinoline carboxylic acid derivative (7-chloro (or fluoro)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid) to form the new fluoroquinolone drug, gemifloxacin as described in Scheme 4.1.

5. MECHANISM OF ACTION AND USES

Gemifloxacin is a third generation, oral broad-spectrum, fluorinated quinolone antibacterial agent. It acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for cellular replication and bacterial growth [7]. It is



SCHEME 4.1 Synthetic pathway for synthesis of gemifloxacin. (a) $CH{=}CH{-}CN$, NaOH, 60 °C; (b) (t-BOC$)_2$O, $CHCl_3$; (c) NaOEt, EtOH, reflux; (d) $NaBH_4$, EtOH, 0 °C; (e) $LiAlH_4$, THF, −5 °C; (f) (t-BOC$)_2$O (dioxane-water), $NaHCO_3$, pH 8.5; (g) (SO_3-pyridine), DMSO, Et_3N, 5 °C; (h) $MeO{-}NH_2 \cdot HCl$, $NaHCO_3$, EtOH–THF, 40 °C; (i) $CH_3{-}CO{-}Cl$, MeOH, 0 °C; (k) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 °C, stirring 30 min at 25 °C, CH_3CN.

well known that *Streptococcus pneumoniae* has been showed mutations in both DNA gyrase and TOPO IV (double mutants), and they are resistant to most fluoroquinolones [8]. Thus, gemifloxacin is considered the only fluoroquinolone which has the ability to inhibit both enzyme systems (dual targeting of both DNA Gyrase and TOPO IV) at therapeutically relevant drug levels in *S. pneumoniae* [7–9]. Further, it has a minimum inhibitory concentration values that are still in the susceptible range for some of these double mutants. The main advantage of gemifloxacin over the older agents of fluoroquinolones is retaining the excellent activity against Gram-negative bacilli and improving Gram-positive activity (including *S. pneumoniae* and *Staphylococcus aureus*) [9,10]. Therefore, gemifloxacin was approved by the Food and Drug Administration (FDA) in April 2003 for treatment of acute bacterial exacerbation of chronic bronchitis, mild-to-moderate pneumonia, and multidrug resistant *S. pneumoniae* as well as community-acquired pneumonia [9,11,12].

6. SPECTROSCOPY

6.1. UV–VIS spectroscopy

The ultraviolet absorption spectra of gemifloxacin mesylate were recorded on A Shimadzu UV-1601 PC double beam spectrophotometer with matched 1-cm quartz cells in water, methanol, 0.1 N hydrochloric acid, and 0.1 N sodium hydroxide solutions. Figure 4.1 shows the recorded absorption spectra of these solutions. The recorded spectra were essentially identical and exhibiting two peak maxima for each spectrum at 266 and 340, 272 and 342, 272 and 344, and 262 and 342 nm for the solutions in water, methanol, 0.1 N hydrochloric acid and 0.1 N sodium hydroxide, respectively. The molar absorptivity of gemifloxacin mesylate was found to be moderately affected by the solvent used. The calculated molar absorptivity in water, methanol, 0.1 N hydrochloric acid, and 0.1 N sodium hydroxide solutions at the two maxima was tabulated in Table 4.1. However, the position of the maxima, as compared to water, was slightly red shifted for methanol and 0.1 N hydrochloric acid solutions and slightly blue shifted for 0.1 N sodium hydroxide solution.

6.2. Fluorescence spectroscopy

Gemifloxacin mesylate was found to be very strongly fluorescent when dissolved in water and moderately fluorescent in 0.1 N hydrochloric acid and 0.1 N sodium hydroxide (the fluorescence intensity of gemifloxacin mesylate in 0.1 N HCl was about twofolds more than that of 0.1 N NaOH).

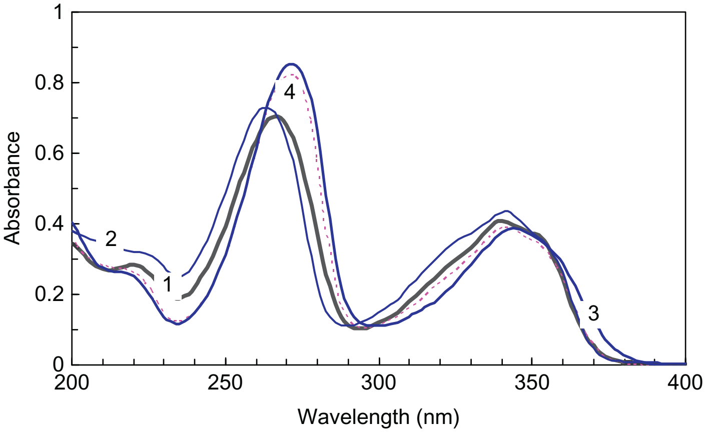


FIGURE 4.1 The ultraviolet absorption spectra of 10 ppm gemifloxacin mesylate in water (1), 0.1 N sodium hydroxide (2), 0.1 N hydrochloric acid (3), and methanol (4) solutions.

TABLE 4.1 The calculated molar absorptivity of gemifloxacin in different solvents

Molar absorptivity (ε)	Water	Methanol	0.1 N HCl	0.1 N NaOH
(ε) at 266–272 nm	36,902	40,975	43,230	38,356
(ε) at 340–344 nm	19,219	19,545	19,409	23,078

Spectrofluorimeter, Kontron SFM 25 equipped with a 150-W xenon high-pressure lamp was used for recording the fluorescence spectrum of gemifloxacin mesylate in water. As shown in Fig. 4.2, the fluorescence spectrum exhibited two excitation maxima at 266 and 342 nm and one emission maximum at 391 nm. The fluorescence intensity obtained at λ_{ex} 266 nm was found to be more (5–25% depending on the solvent used) than that obtained at λ_{ex} 342 nm. Moreover, the position of the emission maximum was red shifted in 0.1 N HCl solution (405 nm) and blue shifted in 0.1 N NaOH solution (390 nm).

6.3. IR spectroscopy

The infrared absorption spectrum of gemifloxacin mesylate was recorded on FT-IR model Spectrum BX spectrophotometer (Perkin-Elmer, USA) using a KBr disc (~2 mg of gemifloxacin mesylate was dispersed in 200 mg KBr). The obtained infrared spectrum is shown in Fig. 4.3, and the assignments of the characteristic bands are tabulated in Table 4.2.

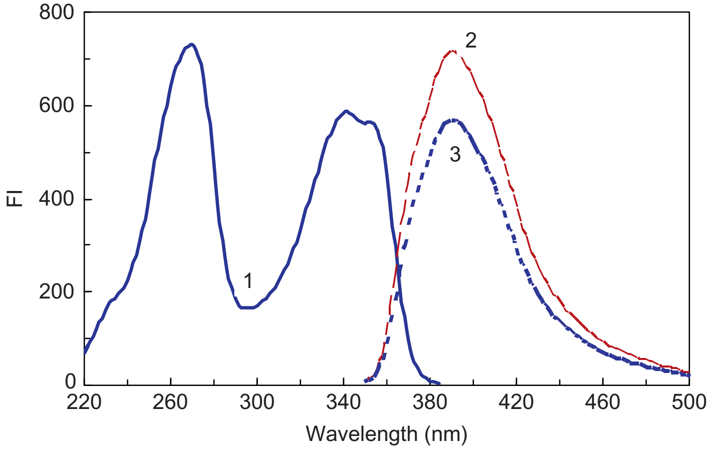


FIGURE 4.2 The excitation (1) and emission spectra (2, 3) of aqueous solution of gemifloxacin mesylate (2 ppm). The emission spectra (2) and (3) were obtained at excitation wavelength of 266 and 342 nm, respectively.

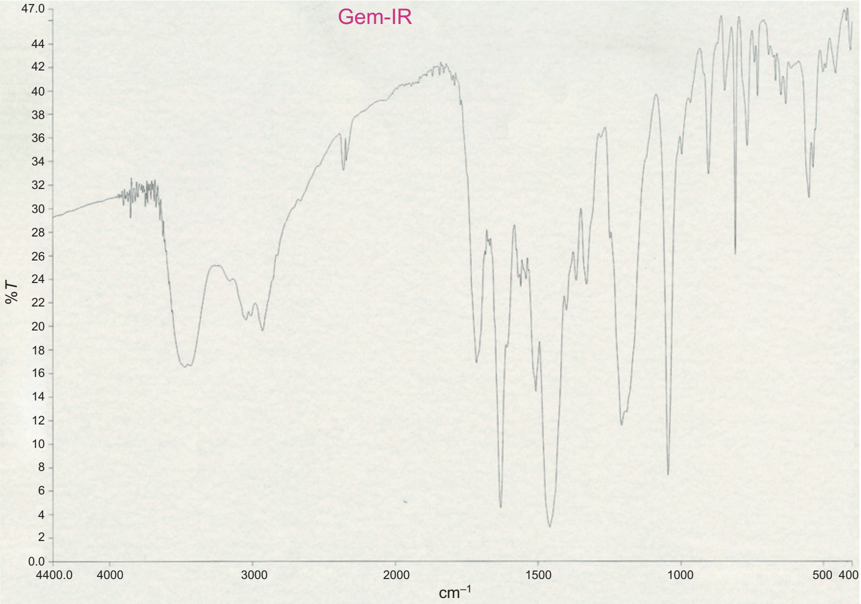


FIGURE 4.3 Infrared absorption spectrum of gemifloxacin mesylate using KBr disc.

TABLE 4.2 Assignments of the characteristic infrared absorption bands of gemifloxacin mesylate

Energy (cm^{-1})	Band assignment
3474	$-NH_2$ stretching mode and –OH hydrogen bonded
2930	–CH stretching mode
2343, 2364	
1718	Carboxylic –CO stretching mode
1631	–CO stretching mode
1458	C=C stretching mode
1300 and below	Fingerprint region

6.4. ^{1}H NMR spectroscopy

The ^{1}H NMR absorption spectrum of gemifloxacin mesylate was recorded on a Bruker-Ultra Shield spectrometer (Bruker Co., USA) at 500 MHz in deuterated water. The obtained ^{1}H NMR spectrum is shown in Figs. 4.4 and 4.5, and the assignments of the observed bands are tabulated in Table 4.3. The four protons of the hydroxyl and amino groups are disappeared in deuterated water.

6.5. Mass spectrometry

The gas chromatography-mass spectrum of gemifloxacin mesylate is presented in Fig. 4.6, and the assignments for the main observed fragments are tabulated in Table 4.4.

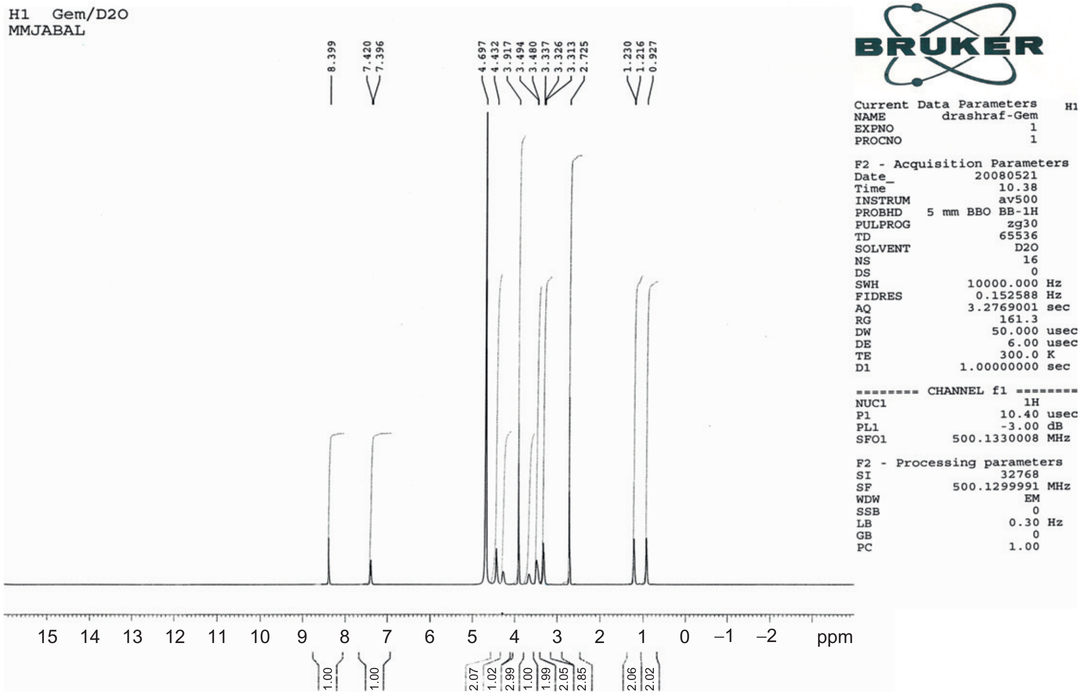
7. METHODS OF ANALYSIS

7.1. UV-analysis

Gemifloxacin mesylate in 0.1 N sodium hydroxide solution was determined in our laboratory using UV spectrophotometry at 342 nm in bulk and its pharmaceutical preparations. Beer's law was obeyed in the concentration range 2.0–20.0 μg/ml at 342 nm, respectively.

7.2. Colorimetric analysis

Gemifloxacin mesylate was oxidized with Fe (III) and determining Fe(II) produced from the oxidation process by its chelation with either 1,10-phenanthroline, 2,2′-bipyridyl, or ferricyanide at 515, 520, and 760 nm,



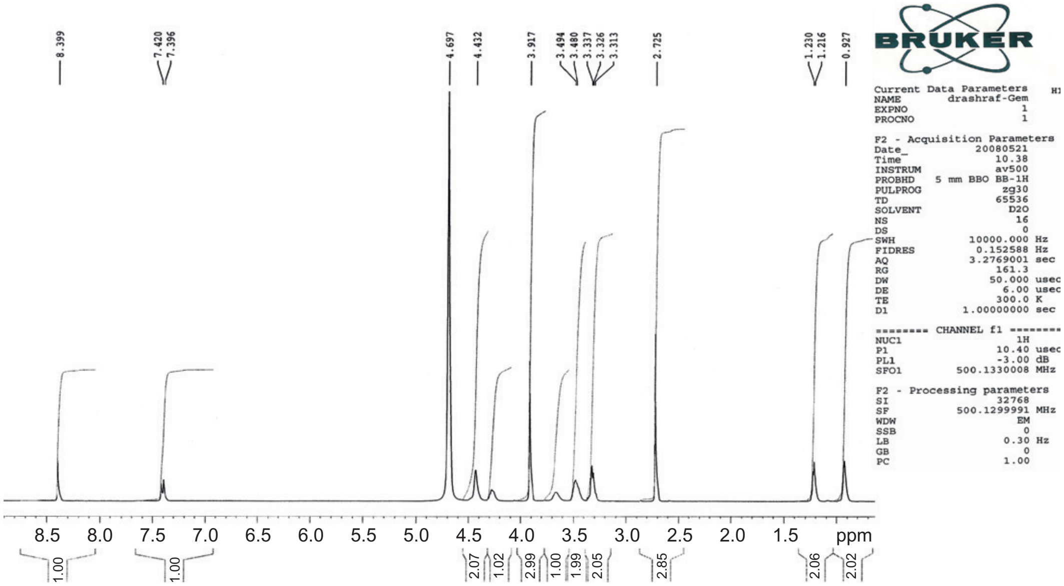
```
Current Data Parameters       H1
NAME           drashraf-Gem
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20080521
Time                  10.38
INSTRUM               av500
PROBHD     5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT                 D2O
NS                       16
DS                        0
SWH             10000.000 Hz
FIDRES           0.152588 Hz
AQ              3.2769001 sec
RG                    161.3
DW                   50.000 usec
DE                     6.00 usec
TE                    300.0 K
D1               1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    10.40 usec
PL1                   -3.00 dB
SFO1            500.1330008 MHz

F2 - Processing parameters
SI                    32768
SF              500.1299991 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

FIGURE 4.4 ^{1}H NMR spectrum of gemifloxacin mesylate (at 500 MHz) in deuterated water.



```
Current Data Parameters     H
NAME           drashraf-Gem
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20080521
Time                  10.38
INSTRUM               av500
PROBHD     5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT                 D2O
NS                       16
DS                        0
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2769001 sec
RG                    161.3
DW               50.000 usec
DE                6.00 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1               10.40 usec
PL1               -3.00 dB
SFO1        500.1330008 MHz

F2 - Processing parameters
SI                    32768
SF          500.1299991 MHz
WDW                      EM
SSB                       0
LB                  0.30 Hz
GB                        0
PC                     1.00
```

FIGURE 4.5 Expanded (3.0 to 7.5 ppm) ^{1}H NMR spectrum of gemifloxacin mesylate (at 500 MHz) in deuterated water.

TABLE 4.3 ^{1}H NMR spectral assignments for gemifloxacin mesylate

Chemical shift (ppm)	Multiplicity	Number of protons	Assignment
0.93	Singlet	2	Cyclopropyl-2-H
1.23	Duplet	2	Cyclopropyl-3-H
2.73	Singlet	3	Mesylate-H
3.31–3.34	Multiplet	2	3-Aminomethyl-H ($-CH_2$)
3.48–3.49	Duplet	2	Pyrrolidinyl-2-H
3.65	Singlet	1	Cyclopropyl-1-H
3.92	Singlet	3	Methoxy-H
4.28	Multiplet	1	Pyrrolidinyl-3-H
4.43	Singlet	2	Pyrrolidinyl-5-H
7.40–7.42	Duplet	1	1,8-Naphthyridine-5-H
8.40	Singlet	1	1,8-Naphthyridine-2-H

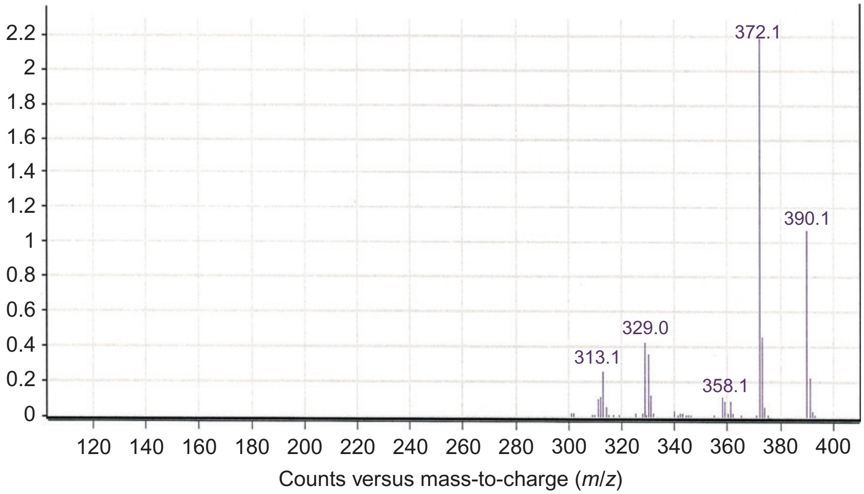


FIGURE 4.6 Gas chromatography-mass spectrum of gemifloxacin mesylate.

respectively [13]. Beer's law was obeyed in the concentration ranges of 3–15, 4–20, and 2–10 μg/ml, respectively. Another method for determination of gemifloxacin mesylate was based on its interaction with ammonium heptamolybdate tetrahydrate resulting in formation of molybdenum blue of λ_{max} 825 nm. The linear dynamic range was 6–30 μg/ml [13].

TABLE 4.4 Gas chromatography mass spectral data of gemifloxacin mesylate

m/z ratio	Relative intensity (%)	Fragment assignment
390.1	49	$[M^+]$
372.1	100	$[M - 18]^+$
358.1	5.5	$[M - 32]^+$
329	19	$[M - 61]^+$
313.1	13.6	$[M - 77]^+$

7.3. Fluorimetric analysis

The direct native fluorescence of propanolic gemifloxacin mesylate solution was used for its assay in the range of 0.05–3 µg/ml in our laboratory. Gemifloxacin mesylate was also determined depending on its ability to form ternary complex with Lanthanide, europium (III) ion in presence of Tris buffer, pH 11–12 [14]. Europium (III) ion enhanced the fluorescence in presence of 0.1 M EDTA, and quenched it in presence of 1% Tween 60. The enhancement and quenching of the fluorescence by europium (III) ion were applicable over the concentration range of 0.1–0.5 and 0.2–0.8 µg/ml of gemifloxacin mesylate, respectively.

7.4. HPLC analysis

High-performance liquid chromatography-tandem mass spectrometry method for the determination of gemifloxacin in human plasma was based on the protein precipitation of plasma samples with acetonitrile containing $[^{13}C^{2}H_3]$ gemifloxacin as an internal standard. The supernatant was injected onto a PLRP-S column without any further clean-up. The mass spectrometer was operated in positive ion mode, and the ions were detected in multiple reaction-monitoring (MRM) mode. The assay requires 50 µl of plasma and is precise and accurate within the range 10–5000 ng/ml [15].

The enantiomers of gemifloxacin mesylate were well enantioseparated on a Crownpak CR(+) chiral stationary phase (CSP). This enantioseparation was the first reported direct separation of the quinolones enantiomers on chiral crown ether coated Crownpak CR CSP [16]. Another more effective CSP derived from (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid was also used for the resolution of racemic gemifloxacin mesylate. The only difference from the previous one was the analytical time [17]. More recently, CSP recently developed by bonding (diphenyl-substituted 1,1′-binaphthyl) crown ether to silica gel was applied to the liquid chromatographic separation of gemifloxacin enantiomers [18]. The resolution of gemifloxacin and its analogs was excellent and even greater than that on the commercial

Crownpak CR(+). Chiral separation of gemifloxacin was performed in analytical counter-current chromatography using (+)-(18-crown-6)-tetracarboxylic acid as CSP. A successful separation of gemifloxacin enantiomers could be achieved using a two-phase solvent system composed of 1-butanol-ethyl-acetate-bis(2-hydroxyethyl)amino tris (hydroxymethyl)methane acetate buffer with a small amount of $^{18}C_6H_4$ [19].

7.5. Capillary electrophoresis

Capillary electrophoresis for the analysis of gemifloxacin enantiomers and its analogs using (+)-18-crown-6-tetracarboxylic acid ($^{18}C_6H_4$) as a chiral selector was performed on urine samples [18]. The presence of alkaline metal ions (Na^+ or K^+ ions) in the sample solution as well as in the run buffer is undesirable due to their strong competitive binding with the chiral selector. The method designed a channel-coupled microchip electrophoresis device to clean up alkaline metal ions from the samples matrix for the chiral analysis of gemifloxacin [20]. In the first channel, the metal ions in the sample were monitored by indirect detection using quinine as a chromophore and drained to the waste. In the second separation channel, gemifloxacin enantiomers, free of the alkaline metal ions, were successfully separated using only a small amount of the chiral selector (50 μM $^{18}C_6H_4$). Another capillary electrophoretic method used a chelating agent, ethylenediaminetetraacetic acid (EDTA), to the run buffer to greatly improve the separation efficiencies and peak shapes in the chiral analysis of gemifloxacin in a saline sample matrix [21]. Capillary electrophoretic method has been also developed for the assay of gemifloxacin in tablets. The method was performed on a 75 μm × 35 cm fused silica capillary using 25 mM H_3PO_4–NaOH running buffer (pH 8.5) at temperature of 25 °C and applied voltage of 12 kV. The detection wavelength was 254 nm and the internal standard was Flumequine. The calibration was linear from 5 to 50 μg/ml for gemifloxacin mesylate [22].

8. CLINICAL PHARMACOKINETICS AND TOXICITY

8.1. Pharmacokinetics

The pharmacokinetic properties of fluoroquinolone antibacterial agents have been well described [23]. Gemifloxacin is rapidly absorbed with a time to maximum plasma concentration ($T_{\max}$) of 0.5–2 h in healthy subjects and displays linear pharmacokinetics over the dose range studied (20–800 mg), with an apparent plasma terminal half-life ($t_{1/2}$) after single or repeated administration of about 8 h. A minimum of 20–30% of the oral dose is excreted unchanged in the urine. Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing. Plasma protein binding of gemifloxacin is low as 70% [24–28].

8.1.1. Absorption and bioavailability

Gemifloxacin, given as an oral tablet, was rapidly absorbed from the gastro-intestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 h following oral tablet administration. The absolute bioavailability of 320 mg tablet was approximately 71%. Following repeat oral doses of 320 mg to healthy subjects, the mean maximal gemifloxacin plasma concentrations ($C_{\max}$) and systemic drug exposure (AUC_{0-24}) were 1.61 ± 0.51 μg/ml (range 0.70–2.62 μg/ml) and 9.93 ± 3.07 μg h/ml (range 4.71–20.1 μg h/ml), respectively.

The pharmacokinetics of gemifloxacin was not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore, the drug may be administered without regard to meals.

8.1.2. Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects was approximately 60–70% and is concentration independent. After repeated oral doses, the *in vivo* plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment did not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 l/kg (range, 1.66–12.12 l/kg).

Gemifloxacin was widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceeded those in plasma. Gemifloxacin penetrated well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, the found concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid, and bronchial mucosa at ~2 h were tabulated in Table 4.5.

8.1.3. Metabolism

Gemifloxacin was metabolized to a limited extent by the liver. The unchanged compound was the predominant drug-related component detected in plasma (~65%) up to 4 h after dosing. All formed metabolites were minor and represents <10% of the administered oral dose; the main metabolites were *N*-acetyl gemifloxacin (the *E*-isomer of gemifloxacin) and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes did not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes was not significantly inhibited by gemifloxacin.

TABLE 4.5 Gemifloxacin concentrations in plasma and tissues (320 mg oral dosing)

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean ± SD)
Plasma	1.40 (0.442) μg/ml	–
Bronchoalveolar macrophages	107 (77) μg/g	90.5 (106.3)
Epithelial lining fluid	2.69 (1.96) μg/ml	1.99 (1.32)
Bronchial mucosa	9.52 (5.15) μg/g	7.21 (4.03)

8.1.4. Excretion

Gemifloxacin and its metabolites were excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61 ± 9.5% of the dose was excreted in the feces and 36 ± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 l/h (range 4.6–17.6 l/h), which indicates that the active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady state following 320 mg to healthy subjects was ~7 ± 2 h (range 4–12 h).

8.2. Toxicity and side effects

A study on 40 healthy male and female volunteers receiving repeated dosing for 7 days with 160 or 320 mg of gemifloxacin (o.d., p.m) demonstrated that the drug has a low potential to cause mild photosensitivity [29].

The cardiac electrophysiological effect of gemifloxacin was investigated, by using conventional microelectrode recording techniques. The data obtained suggested that in the electrophysiological aspect, gemifloxacin had no significant effects at concentrations up to 30 μM (which is 25-fold more than the free plasma concentration after a single therapeutic injection in humans) [30].

The majority of gemifloxacin adverse reactions experienced by patients in clinical trials were considered to be of mild to moderate severity, primarily due to rash (0.8% of patients), nausea (0.3%), diarrhea (0.3%), urticaria (0.2%), and vomiting (0.2%). Most of the postmarketing adverse events reported were cutaneous and most of these were rash. Some of these cutaneous adverse events were considered serious. The majority of rashes occurred in women and in patients under 40 years of age.

8.3. Overdosage and contraindications

Any signs or symptoms of overdosage should be treated symptomatically. No specific antidote is known. In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage; the patient should be carefully observed and treated symptomatically with appropriate hydration maintained. Hemodialysis removes approximately 20–30% of an oral dose of gemifloxacin from plasma. Mortality occurred at oral gemifloxacin doses of 1600 mg/kg in rats and 320 mg/kg in mice. The minimum lethal intravenous doses in these species were 160 and 80 mg/kg, respectively. Toxic signs after administration of a single high oral dose (400 mg/kg) of gemifloxacin to rodents included ataxia, lethargy, piloerection, tremor, and clonic convulsions. The drug is contraindicated in patients with a history of hypersensitivity to gemifloxacin or any of the product components.

8.4. Drug interactions

Administration of repeat doses of gemifloxacin had no effect on the repeat dose pharmacokinetics of theophylline, digoxin, or an ethinylestradiol/levonorgestrol oral contraceptive product in healthy subjects. Concomitant administration of gemifloxacin and calcium carbonate, cimitidine, omeprazole, or an estrogen/progesterone oral contraceptive produced minor changes in the pharmacokinetics of gemifloxacin, which were considered to be without clinical significance. Concomitant administration of gemifloxacin with probenecid resulted in a 45% increase in systemic exposure to gemifloxacin. Gemifloxacin had no significant effect on the anticoagulant effect of warfarin in healthy subjects on stable warfarin therapy.

Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of an antacid containing aluminum and magnesium. Magnesium- and/or aluminum-containing antacids, products containing ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 h before or 2 h after gemifloxacin mesylate tablets (Factive®).

ACKNOWLEDGMENT

The authors are grateful to Dr. Abdullah A. Al-Badr, Professor of medicinal Chemistry, Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia for his help and encouragement.

REFERENCES

[1] C.Y. Hong, Y.K. Kim, J.H. Chang, S.H. Kim, H. Choi, D.H. Nam, et al., J. Med. Chem. 40 (1997) 3584–3593.

[2] M.G. Cormican, R.N. Jones, Antimicrob. Agents Chemother. 41 (1997) 204.

[3] T.A. Davies, L.M. Kelly, D.B. Hoellman, L.M. Ednie, C.L. Clark, S. Bajaksouzian, et al., Antimicrob. Agents Chemother. 44 (2000) 633.

[4] T.A. Davies, L.M. Kelly, G.A. Pankuch, K.L. Credito, M.R. Jacobs, P.C. Appelbaum, Antimicrob. Agents Chemother. 44 (2000) 304.

[5] A.F. Hohl, R. Frei, V. Punter, A. Graevenitz, C. Knapp, J. Washington, et al., Clin. Microbiol. Infect. 4 (1998) 280.

[6] The Merck Index, 13th ed., Merck Co. Inc., Whitehouse Station, NJ, USA, 2001 779.

[7] T.P. Le, Y.Q. Xiong, Drugs Today (Barc). 37 (2001) 401–410.

[8] G.G. Zhanel, S. Fontaine, H. Adam, K. Schurek, M. Mayer, A.M. Noreddin, et al., Treat. Respir. Med. 5 (2006) 437–465.

[9] S.M. Bhavnani, D.R. Andes, Pharmacotherapy 25 (2005) 717–740.

[10] B.K. Yoo, D.M. Triller, C.S. Yong, T.P. Lodise, Ann. Pharmacother. 38 (2004) 1226–1235.

[11] J.M. Blondeau, B. Missaghi, Expert Opin. Pharmacother. 5 (2004) 1117–1152.

[12] I. Morrissey, S. Clark, I. Mathias, J. Med. Microbiol. 49 (2000) 841–844.

[13] M.V. Krishna, D.G. Sankar, Pharma. Rev. 6 (2007) 148–150.

[14] N.F. Youssef, L.I. Bebawy, Bull. Fac. Pharm. (Cairo University) 44 (2006) 215–227.

[15] E. Doyle, S.E. Fowles, D.F. McDonnell, R. McCarthy, White SA, J. Chromatogr. B Biomed. Sci. Appl. 746 (2000) 191–198.

[16] W. Lee, C.Y. Hong, J. Chromatogr. A 879 (2000) 113–120.

[17] M.H. Hyun, S.C. Han, Y.J. Cho, J.S. Jin, W. Lee, Biomed. Chromatogr. 16 (2002) 356–360.

[18] M.H. Hyun, S.C. Han, J. Biochem. Biophys. Methods 54 (2002) 235–243.

[19] E. Kim, Y.M. Koob, D.S. Chung, J. Chromatogr. A 1045 (2004) 119–124.

[20] S.I. Cho, J. Shim, M.S. Kim, Y.K. Kim, D.S. Chung, J. Chromatogr. A 1055 (2004) 241–245.

[21] S.I. Cho, K.N. Lee, Y.K. Kim, J. Jang, D.S. Chung, Electrophoresis 23 (2002) 972–977.

[22] A.A. Elbashir, B. Saad, A. Ali, M. Salhin, K.M.M. Al-Azzam, H.Y. Aboul-Enein, J. Liq. Chrom. Relat. Tech. 31 (2008) 1465–1477.

[23] R.C. Owens Jr., P.G. Ambrose, Med. Clin. North Am. 84 (2000).

[24] A. Allen, E. Bygate, M. Teillol-Foo, S.D. Oliver, M.R. Johnson, C. Ward, J. Antimicrob. Chemother. 44 (Suppl. A) (1999) 137.

[25] A. Allen, E. Bygate, M. Teillol-Foo, S.D. Oliver, M.R. Johnson, C. Ward, J. Antimicrob. Chemother. 44 (Suppl. A) (1999) 133.

[26] A. Allen, E. Bygate, S.D. Oliver, M.R. Johnson, C. Ward, A.J. Cheon, et al., Antimicrob, Agents Chemother. 44 (2000) 1604–1608.

[27] F. Islinger, R. Bouw, M. Stahl, E. Lackner, P. Zeleny, M. Brunner, et al., Antimicrob. Agents Chemother. 48 (2004) 4246–4249.

[28] T. Gee, J.M. Andrews, J.P. Ashby, G. Marshall, R. Wise, J. Antimicrob. Chemother. 47 (2001) 431–434.

[29] M. Vousden, J. Ferguson, J. Richards, N. Bird, A. Allen, Chemotherapy 45 (1999) 512–520.

[30] D. Seop Kim, K.S. Kim, K. Hwan Choi, H. Na, J.I. Kim, W.H. Shin, et al., Drug Chem. Toxicol. 29 (2005) 303–312.