

A-1956 Metabolism and mass balance of [¹⁴C]-Delafloxacin in healthy human volunteers following intravenous administration

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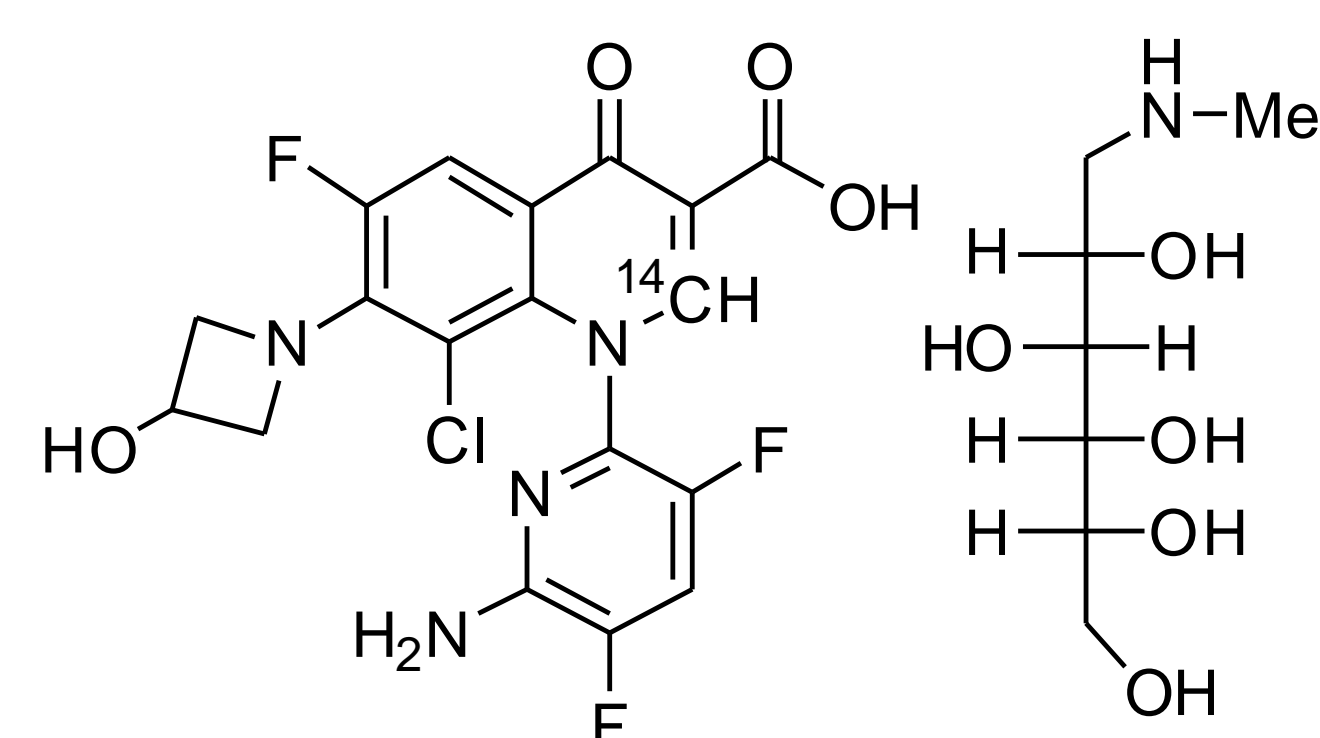
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Introduction

Delafloxacin is a quinolone with antimicrobial activity against gram-positive, gram-negative organisms, atypical and anaerobic organisms. Delafloxacin has potential to treat a variety of infections including complicated skin and skin structure infections, intra-abdominal infections, and hospitalized community-acquired pneumonia. The metabolism and excretion of delafloxacin has been studied in healthy male volunteers following administration of a single intravenous dose of [¹⁴C]-labeled delafloxacin (300 mg, 100 μ Ci).

Test Compound



Source	Quotient Bioresearch Ltd
Physical Form	Solid, meglumine salt
Molecular weight	636.0
Radiochemical Purity	99.8%

API synthesised by Quotient Radiochemicals and IMP prepared at Quotient Clinical under GMP

Methods

The clinical phase of this study was performed at Quotient Bioresearch Clinical Services, Mere Way, Ruddington Fields, Nottingham, NG11 6JS, UK,. The study was approved by the Edinburgh Independent Ethics Committee for Medical Research, and the subjects provided written informed consent prior to study participation.

An intravenous dose of [¹⁴C]-delafloxacin (nominally 300 mg; 3.7 MBq (100 μ Ci)) was administered as a 1 hour infusion to six healthy male subjects. (73 – 104 kg)

Urine and faeces were collected up to 192 hours and the samples analysed for total radioactivity. Whole blood and plasma samples were collected at selected times and analysed for radioactive concentration.

Pharmacokinetic phase

Serial blood samples were collected at selected time-points post dose administration. Concentrations of radioactivity and parent compound in plasma were determined by liquid scintillation counting (LSC) and UPLC-MS/MS (analysis performed at Quotient Bioanalytical Sciences, Fordham) respectively. Plasma concentration versus time data were analysed using PC Modfit (Version 3.0). The kinetic data was characterised by a non-compartmental analysis (NCA).

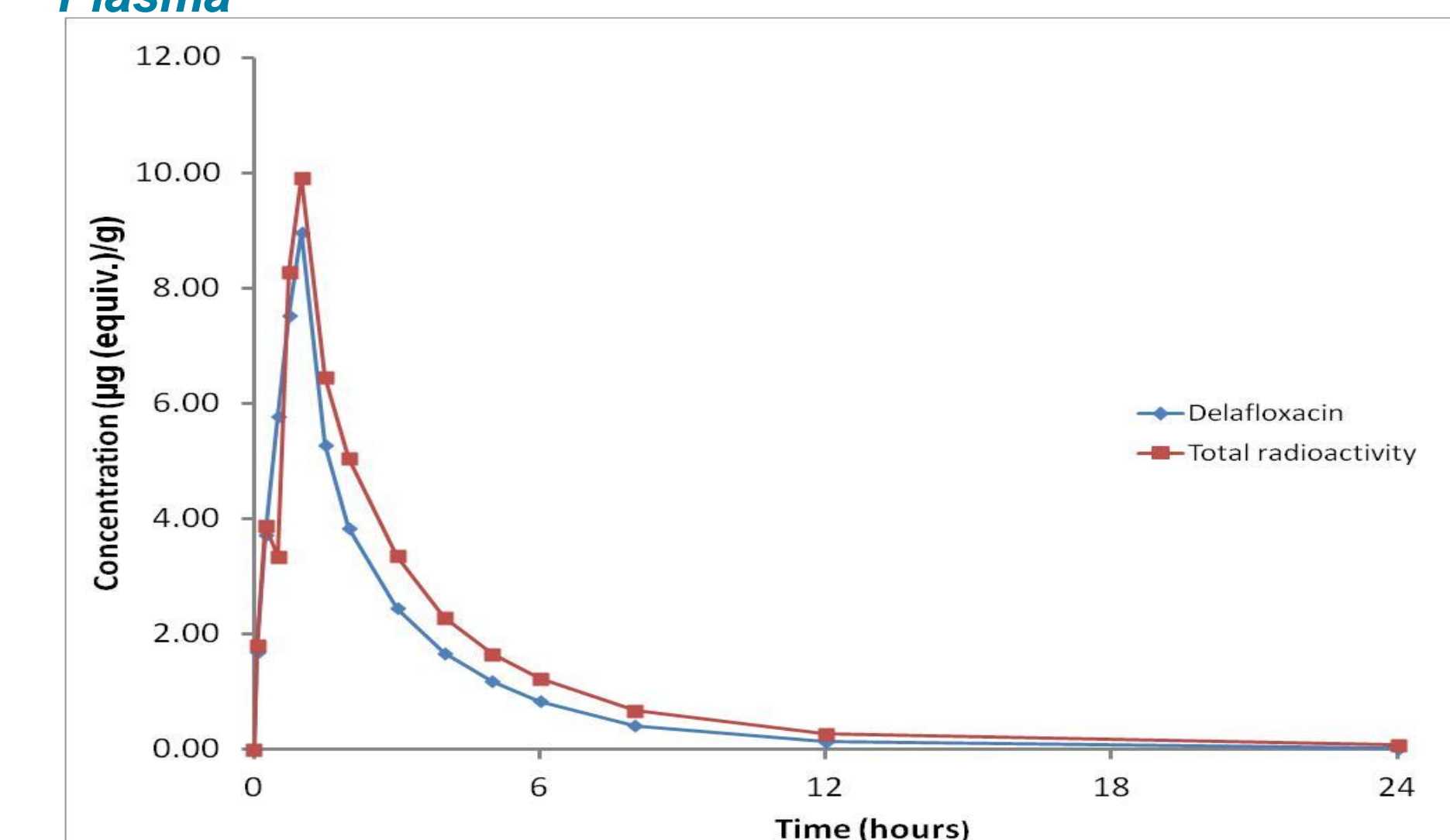
Excretion/balance phase

Urine and faeces samples were collected from six male subjects up to 192 hours post-dose. The radioactivity associated with each sample was determined by quantitative radiochemical analysis (QRA).

Results

Pharmacokinetic phase

Mean Delafloxacin and Total Radioactivity Concentrations in Plasma



Summary of pharmacokinetic parameters for Delafloxacin and total radioactivity

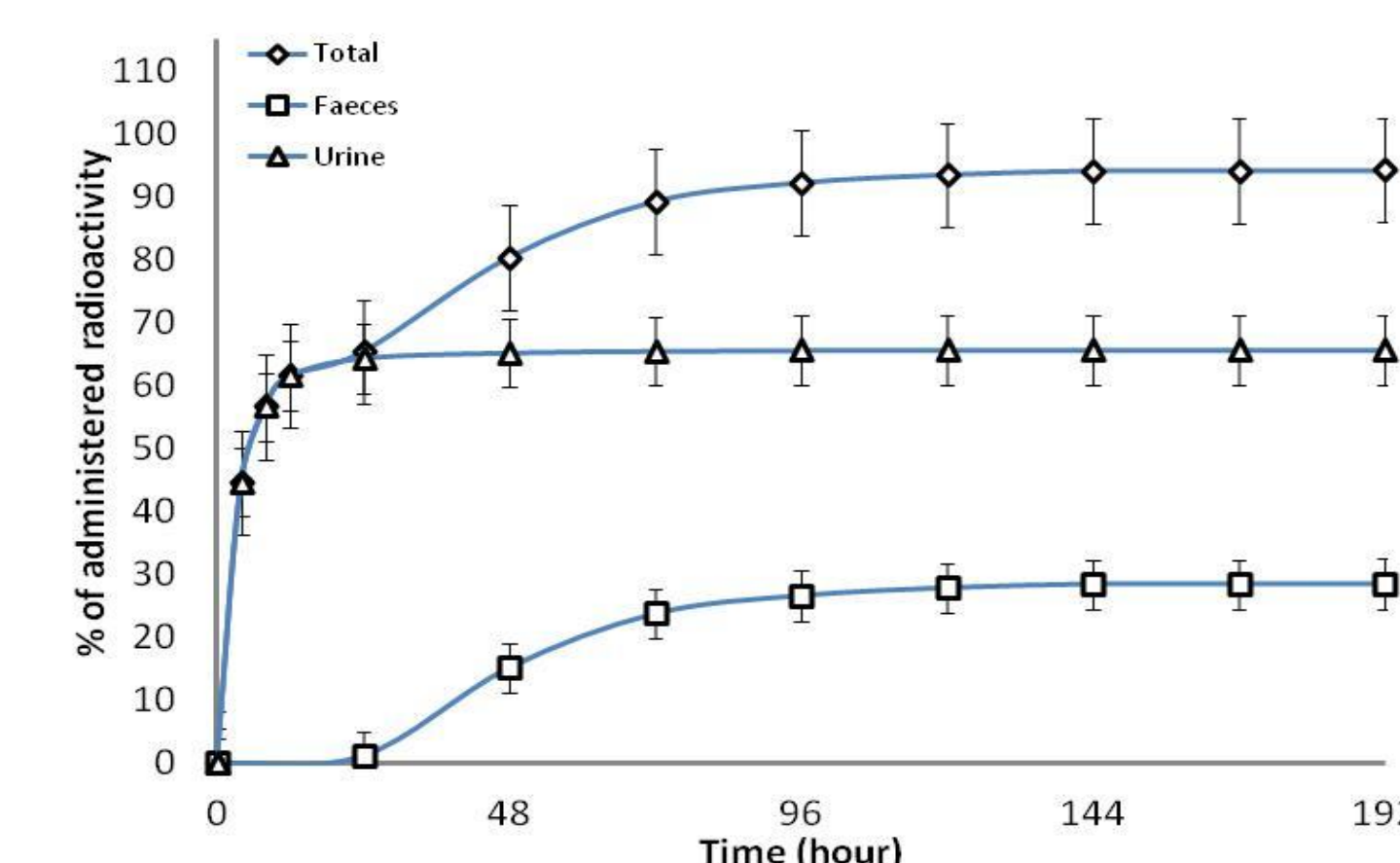
Parameter	Unchanged Delafloxacin (n=6)	Total radioactivity (n=6)
C _{max} (μ g (equiv.)/g)	8.89	9.91
T _{max} (hours)	1	1
AUC _{last} (μ g (equiv.)*hr/g)	22.5	30.0
AUC _{inf} (μ g (equiv.)*hr/g)	22.6	32.6
t _{1/2} (hours)	12.2	35.9

Excretion/balance phase

Sample	Mean recovery of radioactivity (%)	
	0 – 24 hours	0 – 192 hours
Urine	64.39 \pm 4.69	65.69 \pm 4.97
Faeces	0.97 \pm 2.10	28.54 \pm 4.93
Total	65.36 \pm 4.69	94.23 \pm 1.35

Data expressed as percent of total dose (dpm) administered
Data expressed as mean \pm standard deviation (n = 6)

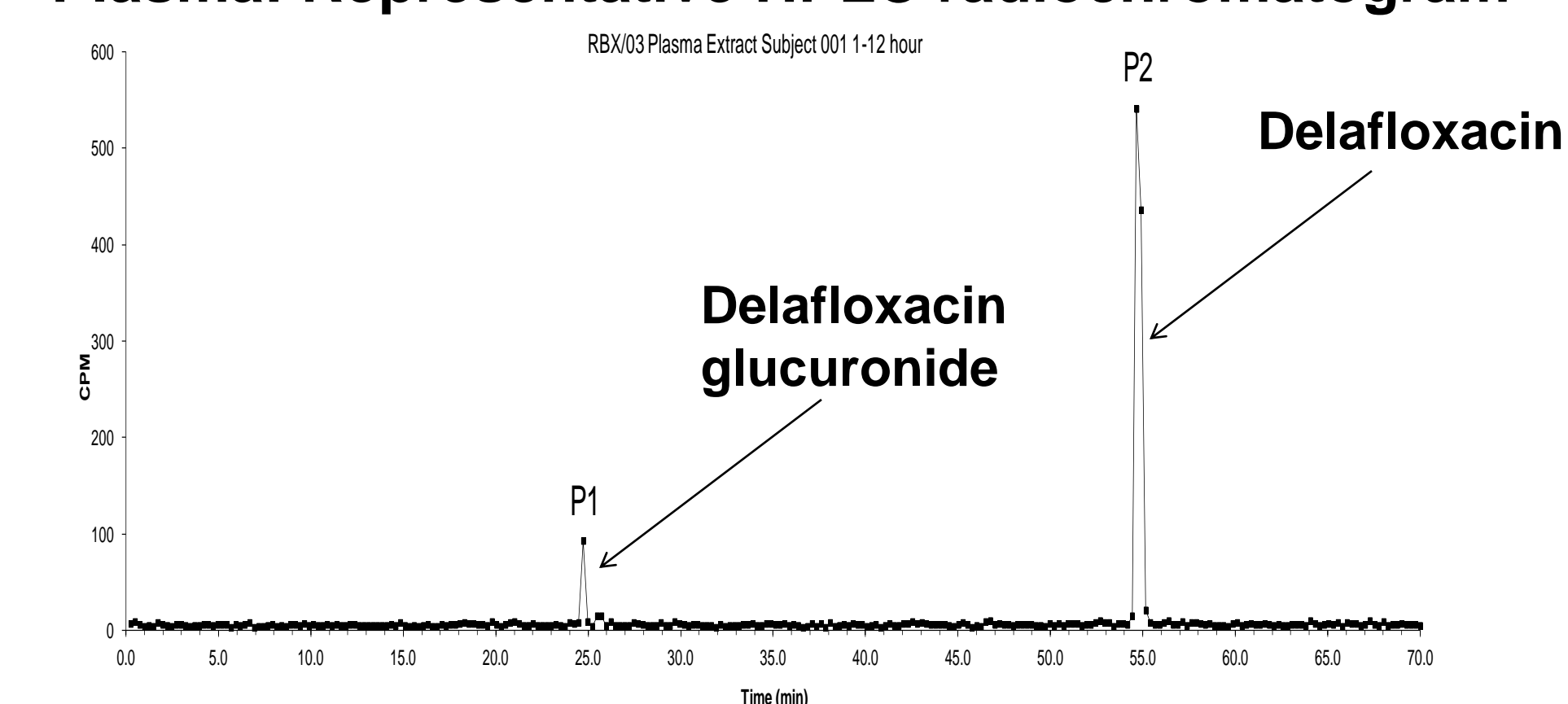
Cumulative excretion of radioactivity



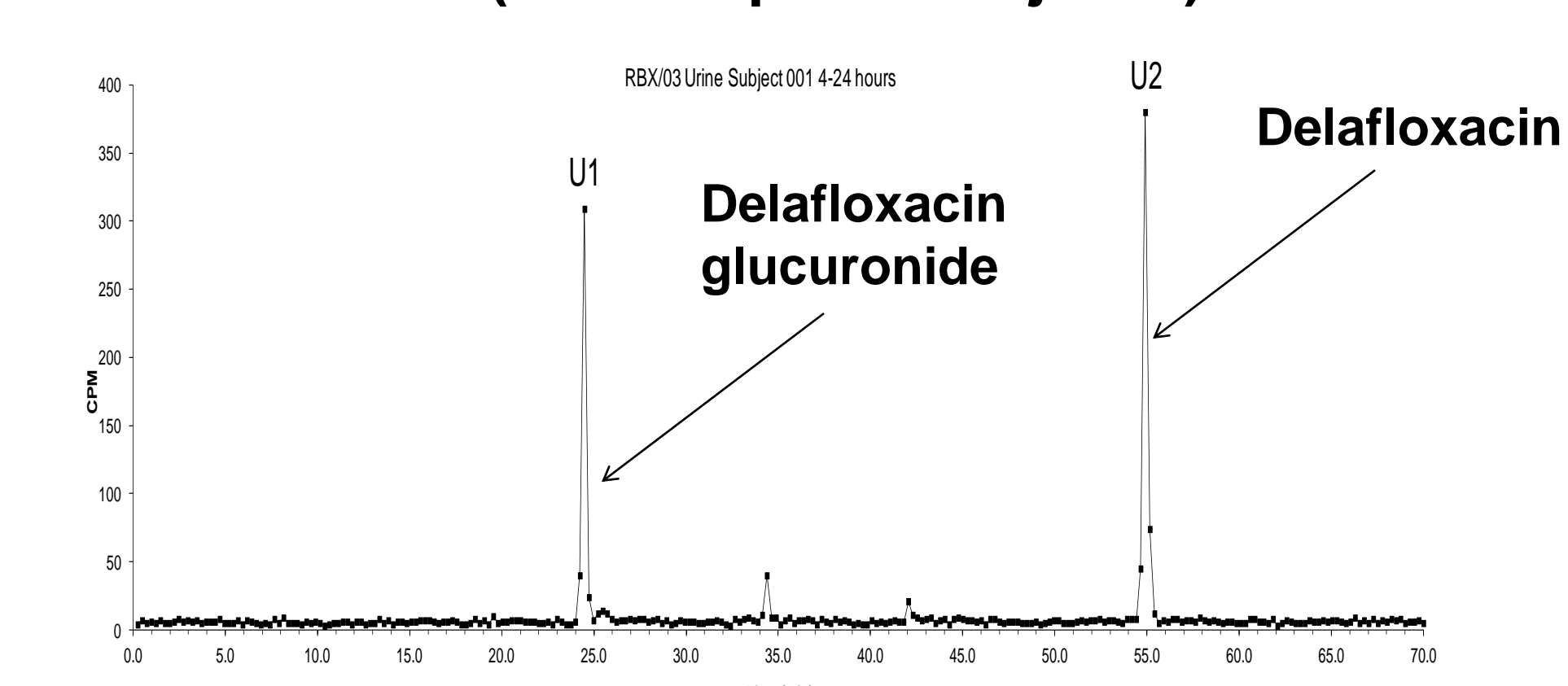
Metabolite identification phase

Two major radioactive components were observed in pooled plasma samples. These were identified as a glucuronide of delafloxacin (P1, U1) and Delafloxacin (P2, U2, F1).

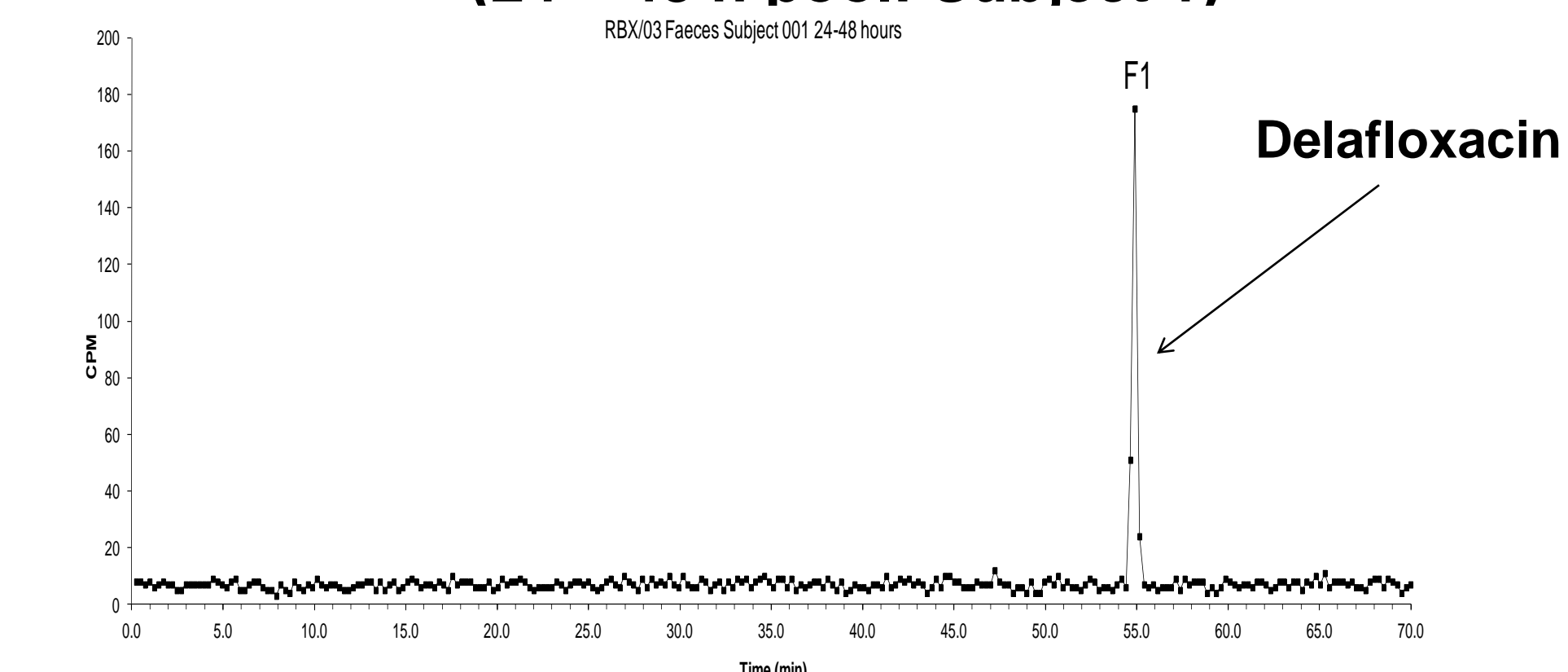
Plasma: Representative HPLC radiochromatogram



Urine: Representative HPLC radiochromatogram (4 – 24 h pool: Subject 1)

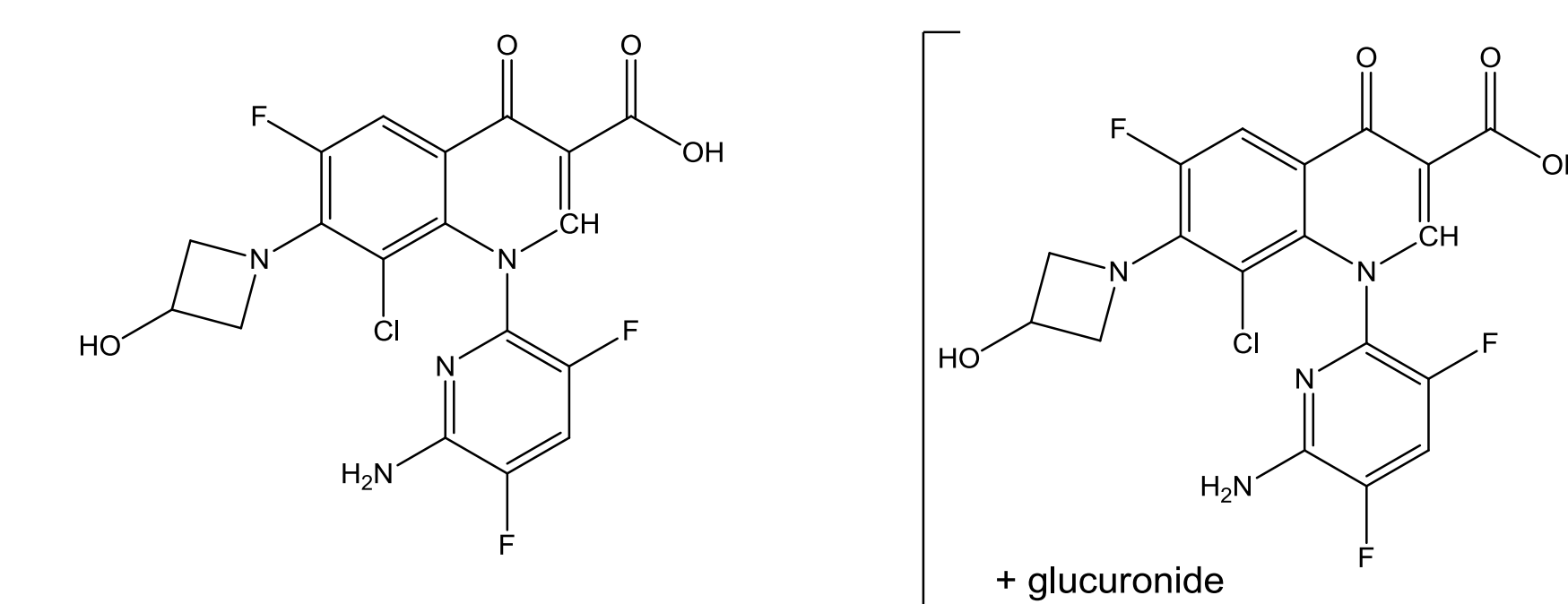


Faeces: Representative HPLC radiochromatogram (24 – 48 h pool: Subject 1)



The major radioactive component observed in urine samples was the glucuronide of delafloxacin accounting for 46% of sample radioactivity between 0 and 6 hours post dose administration. The major radioactive component observed in faeces samples was parent delafloxacin accounting for over 90% of sample radioactivity.

Major radioactive components in plasma, urine and faeces



Delafloxacin
(Urine, Faeces, Plasma)

Glucuronide of Delafloxacin
(Urine, Plasma)

Samples selected for metabolite profiling were analysed by LC-MS/MS using a Finnigan TSQ Quantum Ultra AM (Thermo Fisher Scientific, UK) with in-line fraction collection. A mass spectrometry method incorporating a full scan and multiple reaction monitoring (MRM) was used to confirm the presence of delafloxacin and any additional drug-related components with an exposure (AUC) of more than 10% of the exposure (AUC) of the total radioactivity in plasma in accordance with ICH M3 Guidance

Conclusions

Following a single intravenous (IV) dose of [¹⁴C]-labelled delafloxacin to male human subjects:

- There were no adverse events observed in the six subjects during the study.
- Terminal elimination half-lives measured for radioactivity and delafloxacin in plasma were 35.9 and 12.2 hours respectively.
- Excretion of radioactivity was predominantly via the urine (65.69% dose) with delafloxacin as the major excreted radioactive component.
- Radioactivity excreted in faeces accounted for 28.54% dose and total recovery (urine + faeces) over 192 hours was 94.23%.
- Two major components were observed in plasma samples – delafloxacin and a glucuronide, whilst the major urine metabolite was identified as the glucuronide of delafloxacin