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Development, validation and transfer into a factory environment of a liquid chromatography tandem mass spectrometry assay for the highly neurotoxic impurity FMTP (4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine) in paroxetine active pharmaceutical ingredient (API)

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ABSTRACT

This work describes the development of a liquid chromatography tandem mass spectrometry (LC–MS/MS) assay for a highly toxic impurity, FMTP (4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine), in paroxetine active pharmaceutical ingredient (API), followed by the subsequent validation of the methodology and transfer into a global production/quality control environment. The method was developed to achieve a detection limit of 10 ppb mass fraction of FMTP in paroxetine API. An LC–MS/MS method was chosen because it provided the required sensitivity and selectivity with minimal sample preparation. This paper discusses the issues with transferring such complex methodology to a production environment. Linearity, repeatability and reproducibility of the method were demonstrated. This work shows that it is possible using the same approach that would be used for the transfer of any analytical method from R&D to a manufacturing environment.

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1. Introduction

The contentious issue of highly toxic impurities, and providing general guidance for safe levels of (potentially) toxic impurities in active pharmaceutical ingredients (APIs) has received considerable attention in the recent past.

The Committee for Medicinal Products (CHMP) highlighted concerns that the existing ICH guidance (ICH Q3A(R) [1] and ICH Q3B(R2) [2]) did not adequately address this issue. The CHMP has recently issued a Guideline on the Limits of Genotoxic Impurities [3]. CHMP advocate a generally applicable approach for defining the acceptable risk, which is defined as an additional cancer risk of greater than 1 in 1,00,000 based on a lifetime's exposure to a particular genotoxic impurity. The level of this lifetime exposure is termed the threshold of toxicological concern (TTC) and is equal to an exposure of 1.5 μg/day of the genotoxic impurity. Based on this defined threshold value, appropriate levels of the genotoxic impurity in the API can be then calculated based on the expected daily dose.

Another sub-class of highly toxic impurities that can be encountered in APIs, are 'tremogenic impurities'. These are highly potent impurities that can induce Parkinsonism in humans. These impurities were first encountered in the early-1980s by Langston et al. [4], who were investigating the incidence of chronic Parkinsonism in illicit drug users. They found that the meperidine-analogue "designer-drug" that was being abused by addicts was contaminated by two highly potent impurities; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [5–7] and trace amounts of 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP). Their toxicity was attributed to selective damage of cells in the *Substantia nigra*.

There are two pharmacopoeial APIs that have the potential to be contaminated with tremogenic impurities; pethidine and paroxetine (3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine).

Pethidine can contain trace amounts of MPTP derived from the hydrolytic degradation of the ethyl ester side chain. MPTP has been

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found at levels of 0.5–5 ppm mass fraction [8]. The Ph. Eur. monograph [9] has a production statement and limits for MPTP of 10 ppm mass fraction for non-parenteral use, and 0.1 ppm mass fraction (100 ppb) for parenteral use. It has been reported recently in the literature that the Ph. Eur. liquid chromatography (LC) method with UV detection is capable of control of MPTP at the 10 ppm mass fraction level, but not at the 0.1 ppm mass fraction level [10]. Farina et al. [10] measured MPTP using LC–MS at the sub-ppm mass fraction level and reported that their method was simple, accurate and precise.

Paroxetine can potentially contain trace levels of (4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine) (FMTP) (see Figs. 3 and 4 for structures). FMTP can be a potential reactant/intermediate in the synthesis of paroxetine [11,12]. The Ph. Eur. monographs [13,14] have limits of 1 ppm mass fraction for FMTP, accompanied by a production statement indicating that the test should be performed by LC, coupled with tandem MS (LC–MS/MS) using a suitable validated method.

The biggest challenge facing the pharmaceutical analyst has been the need for the rapid development of extremely sensitive and robust analytical methodologies that can adequately monitor these potentially highly toxic impurities at very low levels. The most important issues are sensitivity, selectivity, and overcoming matrix interference in APIs, and particularly in drug products. The issue of selectivity cannot be overstated as basic understanding of chemistry at the ppm mass fraction level is limited.

Such issues were encountered in the development of the LC–MS/MS assay of FMTP in paroxetine and the approaches taken to overcome these are described in this work. The significant challenges of transferring these very sensitive methodologies developed in R&D laboratories equipped with latest (expensive) state-of-the-art instrumentation requiring highly trained specialist staff into a global production/quality control (QC) environments and regulatory laboratories should not be under-estimated. It is therefore imperative that the analytical methodology developed is robust [15] and rugged [16].

This paper provides details of the validation of LC–MS/MS assay for the measurement of trace levels of FMTP in paroxetine API.

2. Experimental

2.1. Liquid chromatography

An Agilent 1100 chromatography system (Agilent Technologies, Stockport, UK) was used. The column was a Waters Symmetry C_{18} 2.1 mm × 150 mm and 5 μm particle size (Waters Corp., Milford, MA, USA). The flow rate was 0.15 mL/min. Eluent A consisted of deionised water with 0.1% volume fraction trifluoro acetic acid (TFA) (Ultrafine, Manchester, UK), filtered and degassed and eluent B consisted of acetonitrile (Fisher Chemicals, Loghborough, UK) with 0.1% volume fraction TFA, filtered and degassed. Elution started at 25% volume fraction of B and was held for 7 min, increased to 95% volume fraction over 0.5 min, held for 10 min, decreased to 25% volume fraction of B over 0.5 min and was held for 12.5 min. Injection volume was 20 μL.

2.2. Mass spectrometry

LC–MS/MS experiments were carried out on a Micromass Quattro LC triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA), using selective reaction monitoring (SRM), which provides both specificity and enhanced sensitivity. During the course of this work three Micromass Quattro LC instruments were used at three different locations, respectively, one within R&D at GlaxoSmithKline (GSK) and the other two at global GSK manufacturing sites. All three instruments were operated using similar conditions.

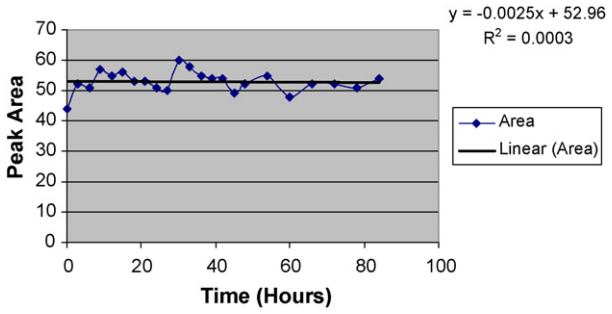

Fig. 1. Stability of a 10 ppb mass fraction FMTP standard in solution for 84 h. Variability of peak area measured is within variability of measurement and method repeatability.

The instruments were operated in positive electrospray ionisation (+ve ESI) mode, with the electrospray probe held at 3.5 kV. The nitrogen desolvation and nebuliser gas flow rates were set to 370 L/h and 80 L/h, respectively. The source temperature was set to 150 °C and desolvation temperature was set to 350 °C for LC–MS. The cone voltage was 16 V and collision energy 10 eV. The SRM transition for FMTP m/z 192.1 to m/z 44.0 was monitored with a dwell time of 1.2 s.

2.3. Standards and sample preparation

A paroxetine reference standard (LRS18) and a paroxetine standard spiked with a known amount of FMTP, namely 143 ppb mass fraction relative to paroxetine (hereafter referred to as 143 ppb FMTP standard), were obtained from GSK's reference materials group. Paroxetine API production batches were used to assay for the potential presence of FMTP. Paroxetine samples were prepared at a mass concentration of 20 mg/mL in water/acetonitrile 75/25 volume fraction with 0.1% TFA volume fraction (diluent A).

In order to determine limits of detection (LOD) and quantitation (LOQ), and linear dynamic range of the LC–MS/MS assay of FMTP, the 143 ppb FMTP standard had to be diluted appropriately. To account for matrix effects, the 143 ppb FMTP standard was diluted with diluent A, containing paroxetine (free of FMTP) at a mass concentration of 20 mg/mL. Thus, irrespective of what levels of FMTP are in the sample, the mass concentration of paroxetine is 20 mg/mL and hence the API matrix effects remain the same. Serial dilutions of the 143 ppb FMTP standard were prepared. Stability of a 10 ppb FMTP mass fraction in paroxetine standard sample was 84 h (which corresponds to the length of the stability study carried out (see Fig. 1)).

3. Validation

3.1. Robustness

For the robustness testing, a design of experiment approach was not utilised, the factors were changed one at a time; and as a consequence no factor interactions were investigated.

The following factors and conditions were investigated:

- Column batch: four Waters Symmetry C_{18} 2.1 mm × 150 mm, 5 μm columns of different manufacturing batches (T81701L 029, T81265D 008, T82801J 019, and T90191L 016) were used for the robustness study.
- Initial percentage of B: two different initial percentage of B were assessed (22% and 24% acetonitrile). FMTP elutes during the ini-

Table 1
FMTP LC–MS/MS SRM method repeatability

	Areas of FMTP peak						
	Injection 1	Injection 2	Injection 3	Injection 4	Average	Standard deviation	CV (%)
$FMTP_{std\ wt1}$	38	36	36	35	36.25	1.26	3.47
$FMTP_{std\ wt2}$	36	37	41	35	37.25	2.63	7.06
$FMTP_{std\ wt3}$	33	34	36	31	33.5	2.08	6.21
$FMTP_{std\ wt4}$	35	34	31	34	33.5	1.73	5.17
$FMTP_{std\ wt5}$	33	37	37	33	35	2.31	6.60
$FMTP_{std\ wt6}$	38	35	37	34	36	1.83	5.07
Average/pooled					35.25	2.02	5.73

tial isocratic step (retention time 3.4 min) therefore there was no need to investigate any other changes in the mobile phase composition.
- Reagents: an alternative manufacturer of acetonitrile and TFA was investigated, ROMIL (Cambridge, UK) and FLUKA (Buchs, Switzerland), respectively. The combination of these two reagents together in the mobile phase was not investigated.

The effect of the changes of these three factors on the retention time of FMTP was monitored.

3.2. Repeatability

The system repeatability was investigated by injecting *n* times the same 10 ppb (mass fraction relative to paroxetine) FMTP standard. Six and 10 replicate injections were performed on the first and second manufacturing site, respectively.

The method repeatability was performed at the first manufacturing site. It was carried out using six separate weighings of the 10 ppb FMTP standard ($FMTP_{std\ wt1}$ to $FMTP_{std\ wt6}$ in Table 1). Each solution prepared was injected four times ($FMTP_{inj1}$ to $FMTP_{inj4}$ in Table 1).

3.3. Reproducibility (ruggedness)

The reproducibility study was carried out using two mass spectrometers, one at a manufacturing site (Irvine) and the other at an R&D site (Harlow). Two analysts performed the limit test measurements on each mass spectrometer on 2 separate days. The analysts prepared two solutions of a 7.5 ppb (mass fraction relative to paroxetine) FMTP standard from one single homogeneous sample of the 10 ppb FMTP (mass fraction relative to paroxetine) standard on each day. Two repeat injections of the samples were performed and the response of the sample was measured relative to the response of the 10 ppb (mass fraction relative to paroxetine) FMTP standard. The experiment was carried out as a fully nested design and the variation of each factor and also the total variation were determined. Fig. 2 represents a schematic of the design used for this study.

3.4. Linearity, limits of detection and quantitation

Two linearity studies were carried out; one on each mass spectrometer at the two different manufacturing sites. The linearity for the measurement of FMTP in paroxetine was investigated over the mass fraction range 2.5–12.5 ppb (25–125% of the 10 ppb mass fraction limit test) and over the mass fraction range of 0.5–20 ppb (5–200% of the 10 ppb mass fraction limit test). The LOD were determined using the results of the linearity experiment (see Section 4).

3.5. Accuracy

The accuracy was determined at four different concentration levels for FMTP in paroxetine: 5 ppb, 10 ppb, 12.5 ppb and 20 ppb (mass fraction relative to paroxetine). For each concentration level three replicate samples were prepared by spiking paroxetine which is free of FMTP at the appropriate level with FMTP standard. The assay was carried out on the paroxetine sample before and after spiking. The difference between the expected and actual result for each level was calculated. Measurements were performed over 2 days and the response of the instrument was checked using the 10 ppb mass fraction FMTP standard.

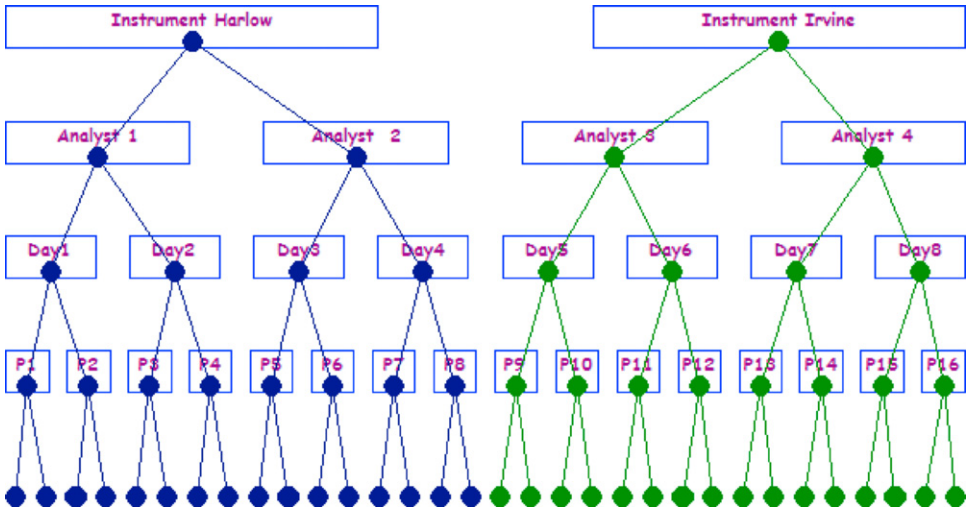

Fig. 2. Schematic of the ruggedness study – a fully nested design – one instrument being on an R&D site (Harlow) and the other on the manufacturing site (Irvine).

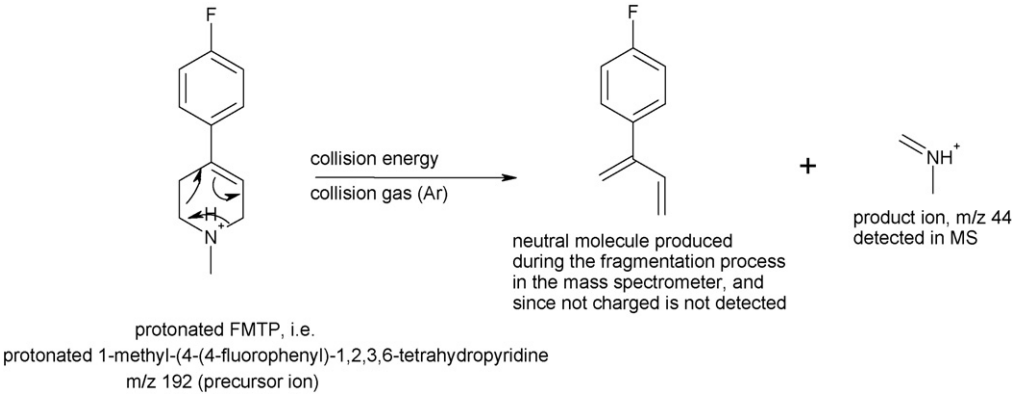

Fig. 3. Fragmentation of FMTP (4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine) in the triple quadrupole mass spectrometer following a Retro–Diels–Alder re-arrangement.

4. Results and discussion

4.1. Development of the LC–MS/MS SRM assay for FMTP

For method development, the approach was taken to develop a method with appropriate sensitivity commensurate with the detection of low levels of FMTP in paroxetine API. A number of methods were investigated including gas chromatography combined with electrochemical and mass spectrometric detection, high performance liquid chromatography (HPLC) and high performance LC combined with tandem MS (LC–MS/MS). The latter approach was found to provide the best balance between sensitivity and specificity, together with relative simplicity. Good sensitivity was also obtained using a complex solid phase extraction method followed by gas chromatography with high resolution mass spectrometry. However, the method was deemed to be impractical for transfer into a manufacturing environment due to its relative complexity. It was decided that the LC–MS/MS approach, which required minimal sample preparation, would provide the best solution. A detection limit of 10 ppb mass fraction of FMTP relative to paroxetine was selected for the assay, as no limit had been set at that time. Subsequently, the Ph. Eur. monograph set a 1 ppm mass fraction limit for FMTP.

Under the HPLC operating conditions described, FMTP elutes at approximately 3.3 min, whereas paroxetine elutes during the wash step, i.e. once the volume fraction of the organic eluent has been increased to 95% (after 7 min). In +ve ESI LC–MS, FMTP gives a protonated molecule ($[M+H]^+$) at m/z 192. Fragmentation in the triple quadrupole mass spectrometer of the protonated molecule (i.e. precursor ion) only gives one predominant product ion at m/z 44. This ion arises by a Retro–Diels–Alder re-arrangement as outlined in Fig. 3. Therefore the SRM transition monitored for the assay was m/z 192 to m/z 44.

To measure trace level impurities (at ppb mass fraction level) by HPLC or LC–MS/MS, either the analyte needs to be enriched, or large amounts of API matrix need to be injected onto the column to obtain sufficient sensitivity. In this case the amount of paroxetine on column is typically 0.4 mg. Hence, there is a significant potential for paroxetine to be present as chemical background (or noise). In addition, in the ion source of the mass spectrometer there is the potential for thermal degradation of protonated paroxetine, or partial fragmentation due to voltages applied to the ion optics, to occur. The thermal fragmentation pathway for paroxetine yields a product ion at m/z 192, which could interfere with the SRM analysis of FMTP, since the m/z 192 formed in the ion source can further fragment in the SRM assay to give an ion at m/z 44 (Fig. 4). Similarly, other impurities, after in-source fragmentation might show a response to the transition monitored. Consequently, it is crucial to develop a chromatographic method able to resolve potential interferences. It is also important that the mass spectrometric methodology, for example, the ion-source conditions (i.e. ion optics voltages, source temperatures and gas pressures) are optimized to minimize unwanted fragmentations of interfering compounds and for maximizing sensitivity for FMTP.

Fig. 5 shows an example of a 10 ppb (mass fraction relative to paroxetine) FMTP standard, where in Fig. 5A the mass spectrometer was tuned for maximum sensitivity for FMTP. However, in this case another interfering compound/impurity, although well-separated chromatographically (eluting at 2.9 min, FMTP eluting at 3.4 min), gave a small response to the transition m/z 192 to m/z 44 monitored. In Fig. 5B, the mass spectrometer was slightly detuned, reducing the sensitivity for FMTP by approximately a factor of 2, but

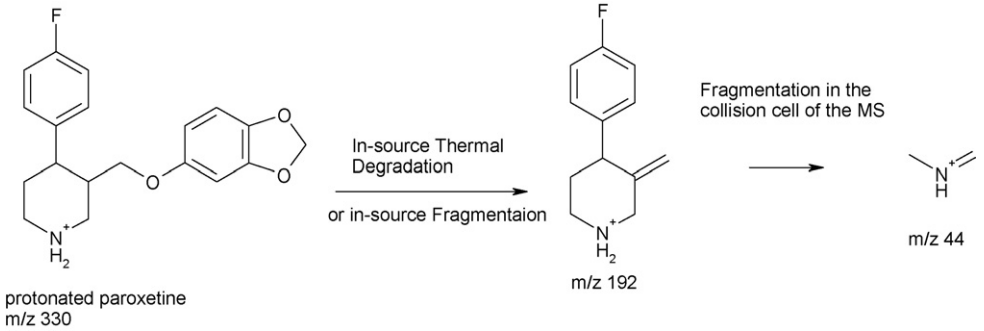

Fig. 4. Schematic for possible interference from paroxetine on the SRM transition monitored for measuring FMTP by SRM. In-source fragmentation of paroxetine followed by in-collision cell fragmentation of the in-source formed ion.

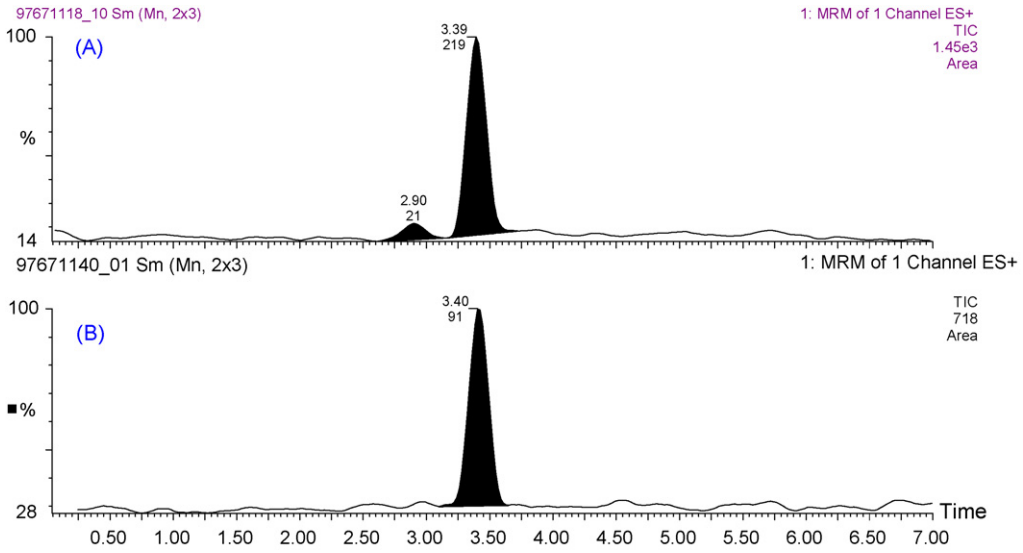

Fig. 5. LC–MS/MS SRM chromatograms for a 10 ppb mass fraction FMTP spiked paroxetine standard—(A) mass spectrometer tuned for optimal sensitivity for FMTP eluting at 3.4 min, small response for interfering compound at 2.9 min – (B) mass spectrometer slightly detuned for FMTP (reducing sensitivity by a factor of 2), interfering compound no longer observed.

the interfering impurity/compound is no longer observed. Since the FMTP LC–MS/MS SRM assay is intended for a manufacturing quality assurance environment, it is essential that any possible ambiguity is removed (e.g. that the SRM chromatogram for an FMTP standard only contains one peak), to ensure maximum reliability. The chromatographic separation was developed such that interference from the in-source paroxetine degradation process as well as any other potential interference was removed.

Additionally, since such a large excess of paroxetine is required to monitor for FMTP at the 10 ppb mass fraction level this could result in contamination of the ion source over time. Therefore, a switching valve was employed to divert the main paroxetine peak to waste (i.e. the flow is diverted to waste during the washing step and is switched back in-line during the re-equilibration to re-condition the ion source of the mass spectrometer).

Fig. 6 shows the results for a typical analysis sequence obtained with the method as developed. Fig. 6A shows the response for a 10 ppb (mass fraction relative to paroxetine) FMTP standard, followed by a subsequent blank injection of solvent (Fig. 6B) and the results obtained for a paroxetine drug substance factory batch (Fig. 6C). The peak for the 10 ppb mass fraction FMTP can be clearly observed with no carryover into the blank and no response detected for FMTP in the paroxetine sample and these data clearly show that the method is accurate at the 10 ppb mass fraction level.

4.2. Validation of the LC–MS/MS SRM assay for FMTP

4.2.1. System suitability

For system suitability the 10 ppb (mass fraction relative to paroxetine) FMTP standard is used. The system is deemed acceptable when the retention time of FMTP is between 3.0 and 4.0 min and the peak area observed is at least 20 mV s (this may change between instruments).

4.2.2. Robustness

During evaluation of method robustness, four columns utilising different batches of stationary phase (from the same supplier) were used and they showed retention times between 3.0 and 3.5 min. There was no significant shift in retention time observed on a single column after at least 500 injections. The method was found to be susceptible to changes in the initial percentage of B; retention times were only slightly affected, but a noticeable deterioration in the peak shape for FMTP and increase in baseline noise was observed. Hence, it is important to use the initial percentage of B specified in the method and to check that the peak shape for FMTP is similar to that shown in the typical chromatogram (Figs. 5B and 6).

4.2.3. Repeatability

On the first manufacturing site the system repeatability experiment for six replicate injections of the same 10 ppb (mass fraction relative to paroxetine) FMTP standard gave an average peak area of 47.8 mV s (range 42–52 mV s) with a standard deviation of 4.8 mV s. The coefficient of variation, calculated according to: $C_v = s/\bar{x} \times 100$, where s is the standard deviation of the peak area and $\bar{x}$ is the arithmetic mean of the peak area, was found to be 10.1%. On the second site, results from 10 replicate injections of the same 10 ppb FMTP standard gave an average peak area of 481 mV s with a standard deviation of 25 mV s and a coefficient of variation of 5.2%. In both cases, the system repeatability obtained is acceptable for such a sensitive assay.

The method repeatability was carried out by injecting four times each of the six separate weighings of the 10 ppb (mass fraction relative to paroxetine) FMTP standard (Table 1). The coefficient of variation for "between sample measurements" (the variability associated with a single prep and single injection estimated through an analysis of variance) was 6.60% (i.e. for $FMTP_{wt1}$ to $FMTP_{wt6}$), and was 5.73% on average for "between injection measurements" (Table 1).

4.2.4. Reproducibility (ruggedness)

The reproducibility study was carried out as a fully nested design and the variation of each factor and also the total variation were determined. The results are shown in Figs. 7 and 8. For instrument 1/analyst 1/day 1/sample preparation 1 and 2, results for only 1 injection were obtained.

A nested model was fitted to the data: instrument, analyst nested within instrument, day nested within analyst, sample preparation within day and injection within preparation. From Fig. 8 it can be seen that analyst and sample preparation gave the largest sources of variation. This is probably not surprising, given the sen-

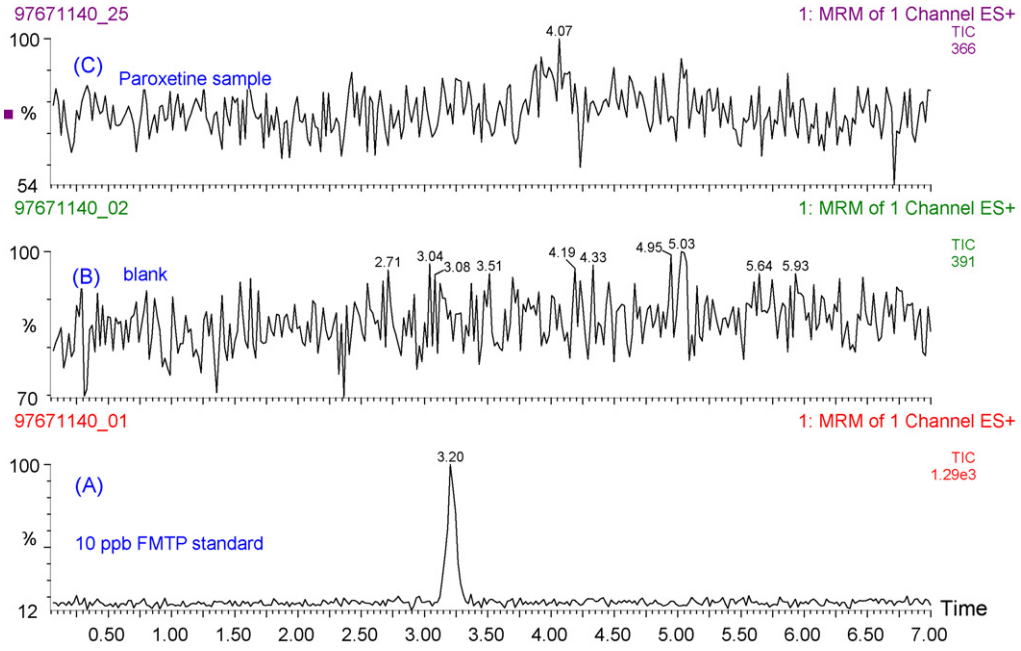

Fig. 6. LC–MS/MS SRM chromatograms monitoring the transition m/z 192 to m/z 44 – (A) 10 ppb mass fraction FMTP standard (in Paroxetine), (B) solvent blank and (C) paroxetine drug substance factory batch.

sitivity of the method. The %R.S.D. of ppb results performed on the same day, by the same analyst on the same equipment is 12% whilst the %R.S.D. allowing for changes in day, analyst and instrument is estimated as 20% (though clearly assessment of variability between instrument is extremely limited with only two being assessed). From Fig. 7 it is seen that larger variation is seen between results on instrument 2. It could be due to a number of factors relating to different modes of working between R&D and manufacturing environment. As with environmental analysis, technique is very important and even the most robust methodologies struggle to overcome the problems of poor technique, transient contamination, etc. This comparative study was carried out very early in the method transfer process and since the purpose of this assay was to measure very low levels of FMTP compared to a 10 ppb (mass fraction relative to paroxetine) reference standard (limit test), the variance was deemed to be acceptable.

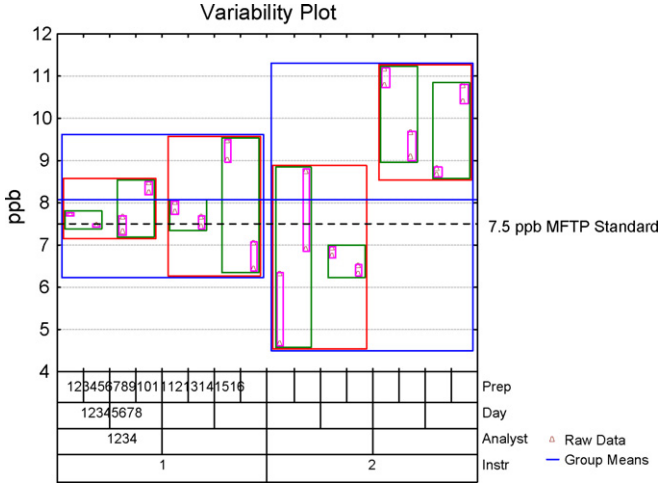

Fig. 7. Reproducibility study results—variation of results observed between instruments, analysts, day of measurement, sample preparation and repeat injection.

4.3. Linearity, limits of detection and quantitation

The least square method was used to calculate the linear parameters of the calibration curves for the two linearity studies. The correlation coefficients (R^2) were 0.987 and 0.995 (see Fig. 9) over the mass fraction ranges of 2.5–12.5 ppb and 0.5–20 ppb, respectively. Fig. 10 shows the predicted versus residuals plot for the linear regression associated with the latter correlation coefficient. The absence of any pattern suggests that there is no evidence that the model is non-linear.

A correlation coefficient value of 0.990 is the acceptance criteria for impurities recommended by the ICH guidelines. However, given the low levels of analyte to be determined (10 ppb mass fraction) and the fact that this was a limit test, this was deemed to be acceptable.

The detection limit obtained is obviously dependant on the mass spectrometric response (i.e. sensitivity) and therefore the two instruments will give different absolute detection limits. However,

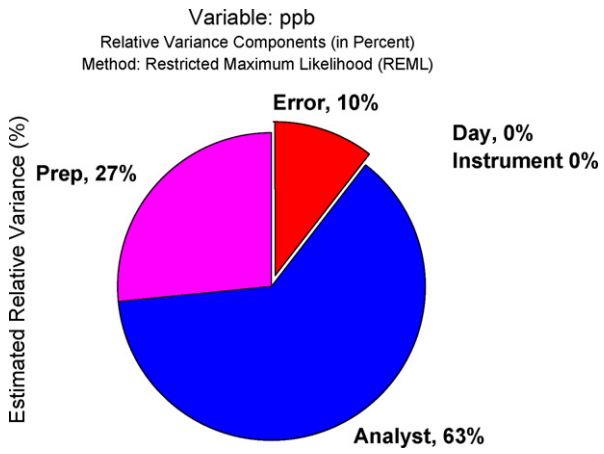

Fig. 8. Sources of variance for the reproducibility of the FMTP LC–MS/MS SRM method.

Table 2
Accuracy and recovery for the measurement of FMTP by LC–MS/MS SRM

Samples—mass fraction of FMTP based on gravimetric preparation	Peak area			Average peak area	Recovery (%)	Calculated (measured) FMTP mass fraction (ppb)
	Injection 1	Injection 2	Injection 3			
10 ppb FMTP (day 1)	37	44	42	41		
10 ppb FMTP (day 2)	44	44	41	43		
5 ppb spiked (day 1)	28	24	24	25.3	123.6	6.2
10 ppb spiked (day 1)	50	47	45	47.3	115.4	11.5
12.5 ppb spiked (day 2)	60	61	60	60.3	112.2	14.0
20 ppb spiked (day 2)	98	95	99	97.3	113.2	22.6

this is not important as long as the 10 ppb (mass fraction relative to paroxetine) limit defined for this method is reproducibly attainable. For instrument 1, where the 10 ppb FMTP standard gave a peak area of about 25 mV s (i.e. at the lower limit of what has been defined for system suitability), the regression line was $y = 2.8x - 0.6$ (standard deviation at the intercept 2.16), and the LOD according to the equation: $LOD = 3.3\sigma/s$, was 2.5 ppb mass fraction FMTP (where σ = standard deviation of the intercept and s = slope of the regression line). For instrument 2, which gave a peak area of about 400 mV s for the 10 ppb FMTP standard, the LOD was determined to be 0.2 ppb mass fraction relative to paroxetine.

The LOQ, according to the equation: $LOQ = 10\sigma/s$, was 7.7 ppb mass fraction FMTP for instrument 1 and the LOQ for instrument 2 is 0.5 ppb mass fraction FMTP relative to paroxetine.

4.4. Accuracy

Recoveries for the spiked samples (versus the 10 ppb – mass fraction relative to paroxetine – reference standard) are given in Table 2.

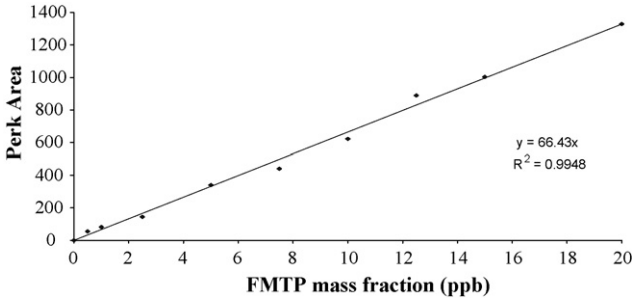

Fig. 9. Linearity of FMTP assay by LC–MS/MS SRM for 0.5–20 ppb mass fraction relative to paroxetine.

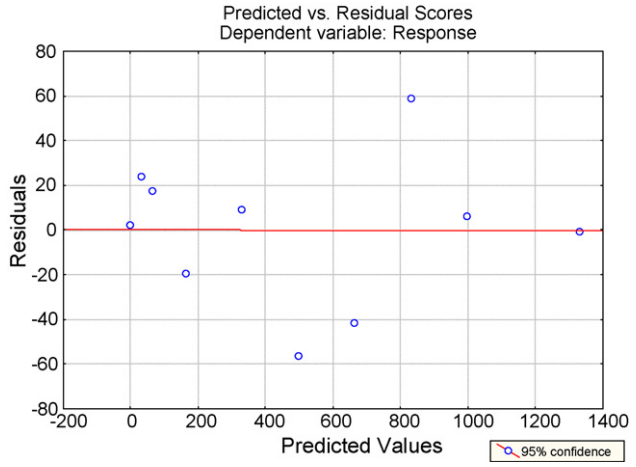

Fig. 10. Predicted versus residuals plot.

The differences between the spiked samples and the reference are within four times the standard deviation on the average peak area (i.e. 4×1.53) determined for the repeatability of the method (Table 1) for each concentration level. This is deemed acceptable for accuracy for a highly sensitive method operating in the ppb mass fraction range.

4.5. LC–MS/MS SRM assay for FMTP in paroxetine API factory batches

As part of the validation, five paroxetine API factory batches were analysed for FMTP content. For all the batches, FMTP levels were below the LOQ of instrument 2, i.e. 0.5 ppb mass fraction.

5. Conclusion

The method transfer detailed was similar to that of a standard method transfer (operating at ICH Q3A levels), that would be carried out for any analytical method transferring into a manufacturing environment. The method showed acceptable repeatability and linearity and was deemed to be suitable for use as a limit test for the detection of levels of FMTP in excess of 10 ppb mass fraction; in paroxetine API batches in a manufacturing environment. This validation was carried out on one model of manufacturer's triple quadrupole mass spectrometer and a similar process would have to be carried out to validate the assay on a different instrument with initial identification of the critical tuning parameters and subsequent optimisation of the parameters.

The challenges of developing, validating and transferring these extremely sensitive methods (ppm, or in this case ppb mass fraction) into a routine, factory environment are significant. In addition, the pharmaceutical industry has no long-term experience in the use of these methodologies within the factory environment. Whether this is a viable option, without significant investment in technology and analytical skill sets, remains open to debate.

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