Scientific paper

Second-Order Derivative UV Spectrophotometric Method for the Determination of Fesoterodine and Comparison with LC, CE and LC-MS/MS in Commercial Extended-Release Tablets

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Abstract

The present work describes a second-order derivative UV spectrophotometric method for determination of a potent antimuscarinic drug, fesoterodine, in extended-release tablets. The method was developed and satisfactory validated according to ICH guideline with respect to specificity, linearity, precision, accuracy, and robustness. The response was linear in the concentration range of 2–24 μg mL^{-1} (r^2 = 0.9999, n = 7) at wavelength 228 nm, which was the zero crossing point of excipient solutions. The detection and quantitation limits were 0.38 and 1.27 μg mL^{-1}, respectively. Precision and accuracy data evaluated by relative standard deviation were lower than 2%. The method proved to be robust by a Plackett-Burman design evaluation. It is simple, it has low cost, and it has low use of polluting reagents. Therefore, the proposed method was successfully applied for the quantitative analysis of fesoterodine in commercial tablets, and the results were compared to validated methods by liquid chromatography, capillary electrophoresis and liquid chromatography-tandem mass spectrometry showing non-significant difference (P > 0.05).

Keywords: Fesoterodine / Derivative UV spectrophotometry / Pharmaceutical analysis / Method validation / Extended-release tablets

1. Introduction

Overactive bladder (OAB) is a lower urinary tract disorder characterized by urinary urgency, with or without urgency incontinence, and usually with increased daytime frequency and nocturia.[1] The initial treatment of OAB consists of behavioral and lifestyle measures to control the symptoms. Antimuscarinic agents are the primary pharmacologic treatment of OAB and are generally safe and effective for symptom relief. Combining behavioral interventions and pharmacotherapy might enhance the therapeutic benefit.[2,3]

Antimuscarinic medications, aimed at blocking cholinergic receptor activity in the bladder, are the primary pharmacotherapeutic options for OAB.[4] Fesoterodine (FESO) is a novel, competitive, muscarinic receptor antagonist that has recently been approved for once-daily oral administration of extended-release tablets in patients with OAB.[5] FESO, a hydrophilic basic drug, and fumarate, its corresponding acidic counter-ion have a molecular weight of 527.66 g mol^{-1} and it is freely soluble in water. The molecular formula is $C_{30}H_{41}NO_7$ and chemical structure is shown in Figure 1.

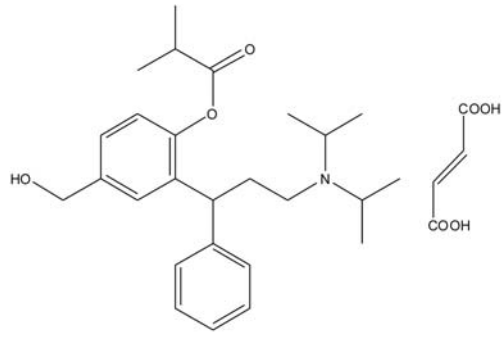

Figure 1. Chemical structure of fesoterodine fumarate.

For the analysis of FESO in extended-release tablets, some analytical methods have been developed by our research group. Recently, a stability-indicating liquid chromatography (LC) method was developed and validated for determination of FESO in commercial tablet dosage forms using a monolithic column.[6] Moreover, for the fast determination of the drug in tablets with very low levels of residues produced, we also validated a specific and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.[7] Another stability-indicating method performed by capillary electrophoresis technique was also developed and validated for FESO determination in quality control analysis.[8]

For routine analysis, a simple, rapid, and cost-effective analytical method is preferred. Spectrophotometric methods are the most commonly used techniques and continue to enjoy wide popularity. The common availability of the instrumentation, the simplicity of procedures, speed, precision and accuracy of the technique still make spectrophotometric methods attractive.[9] Also, spectrophotometric methods of analysis are more economic and simpler, compared to methods such as chromatography and electrophoresis, and can provide a very useful alternative for routine analysis of pharmaceutical formulations.[10–13]

Derivative spectrophotometry is an analytical technique which consists in the differentiating of normal spectrum by mathematical transformation of spectral curve into a derivative (first- or higher derivatives). This technique usually improves resolution bands, eliminates the influence of background or matrix and provides more defined fingerprints than traditional ordinary or direct absorbance spectra, since it enhances the detectability of minor spectral features.[14] Recently, a revision about the derivative UV/visible spectrophotometry was published, describing the advantages of the method, including the application to pharmaceuticals.[9]

In the current literature, there is no publication concerning UV-spectrophotometric determination of FESO. As an alternative to the existing methods, the purpose of this work is to present the development and validation of an useful, simple, fast, inexpensive and environmental friendly second-order derivative UV spectrophotometric (2D-UV) method for routine analysis of FESO in extended-release tablets. The validation procedure was carried out according to the International Conference on Harmonization (ICH) guideline.[15] Responses obtained by validated 2D-UV method was compared to published LC, CE, and LC-MS/MS methods, contributing to establish new alternatives with advantages for the quality control of the pharmaceutical formulations and assuring the therapeutic efficacy.

2. Experimental

2. 1. Chemicals and Reagents

FESO fumarate reference substance was purchased from Toronto Research Chemicals Inc (Toronto, ON, Canada). Toviaz® (Pfizer Inc, Zwickau, Germany) extended-release tablets, containing 8 mg of FESO fumarate, were obtained from commercial sources. All chemicals used were of pharmaceutical or special analytical grade. Ultrapure water (Milli Q Gradient System, Millipore Corp., Bedford, MA, USA) was used for all the analyses. FESO dosage form was labeled to contain the following excipients: glyceryl behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

2. 2. Apparatus and Experimental Conditions

2. 2. 1. 2D-UV Method

An UV-Vis UV-1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan) with 1 cm quartz cells was employed. UVProbe 2.33 software was used for instrument control and data acquisition. The second-order derivative spectra of solutions were recorded at a fast scan speed with a fixed slit to lead to a spectral resolution of 1 nm. The spectra were obtained by instrumental electronic differentiation using a wavelength interval ($\Delta\lambda$) of 4 nm in the range of 200–300 nm. The determinations were made at 228 nm. All analytical responses obtained were multiplied by 100 (scaling factor of 100). The spectrophotometric measurements were recorded by using water as a blank solution.

2. 2. 2. LC Method

A LC $10A_{VP}$ system (Shimadzu, Kyoto, Japan) was used and the analytical method was performed according to a previously published paper.[6] The PDA detector was set at 208 nm and peak areas were integrated automatically by computer using a Class VP® V 6.12 software program. The experiments were carried out on a reversed-phase Phenomenex (Torrance, CA, USA) Onyx C_{18} monolithic column (100 mm × 4.6 mm id). The LC system was operated isocratically at 45 °C using a mobile phase of acetonitrile-methanol–0.03 mol L^{-1} ammonium acetate (pH 3.8) (30:15:55, v/v/v), run at a flow rate of 2.4 mL $min^{-1.}$ The injection volume was 10 µL for both standard and samples.

2. 2. 3. CE Method

CE experiments were performed on an Agilent ^{3D}CE apparatus (Agilent Technologies, Waldbronn, Germany). CE ChemStation software was used for instrument control, data acquisition and analysis. All experiments were carried out on a fused-silica capillary with 50 µm i.d. and 72 cm of effective length (total length 80.5 cm), thermostatized at 35°C, and detection at 208 nm using a photo-

diode array (PDA) detector. The method employed 0.01 mol L^{-1} sodium phosphate buffer at pH 6.5 as background electrolyte (BGE) and epinastine as internal standard (IS).[8] At the beginning of each working day, the capillary was conditioned by rinsing with 0.1 mol L^{-1} NaOH for 20 min, followed by water for 15 min, and then with running electrolyte solution for 20 min. To achieve high migration time reproducibility between injections, before each injection the capillary was reconditioned with 0.1 mol L^{-1} NaOH (2 min), water (1 min), and a running BGE solution (2 min). Samples were injected using the hydrodynamic injection for 5 s at 50 mbar and a constant voltage of 30 kV was applied during the analysis. Since electrolysis can change the EOF and affect the migration time, efficiency and selectivity, after each three injections the running electrolyte solution was replaced by a fresh solution.

2. 2. 4. LC-MS/MS Method

The published LC-MS/MS method was performed on a Shimadzu LC system equipped with an SCL-$10A_{VP}$ system controller, an LC-$10AD_{VP}$ quaternary pump, a DGU-14A degasser, a SIL-$10AD_{VP}$ autosampler, and a CTO-$10AD_{VP}$ column oven.[7] The triple quadrupole mass spectrometer (Micromass UK Ltd., Manchester, UK), model Quattro LC, was equipped with an electrospray (ESI) source in positive mode. Data acquisition and analysis were performed using the Masslynx software (v 3.5). Chromatography was carried out on a Phenomenex Luna C8(2) column (50 mm × 3.0 mm i.d., 3 μm). The LC system was operated isocratically at controlled temperature (45 °C) using a mobile phase of methanol–0.1% formic acid (90:10, v/v), run at a flow-rate of 0.2 mL min^{-1} with an injection volume of the 10 μL. The best MS response was obtained with capillary voltage, extractor voltage, RF lens voltage, source temperature and ESI probe temperature of the 3.5 kV, 3 V, 0.4 V, 120 and 500 °C, respectively. The cone voltage was 45 and 35 V and the collision energy 31 and 29 eV for FESO and manidipine (IS), respectively. The mass spectrometer was set up in multiple reaction monitoring (MRM) mode, monitoring the transitions 412.2 → 223.0 and 611.1 → 167.0, for FESO and IS, respectively.

2. 3. Preparation of Reference Solution

The stock solution of FESO was prepared by weighing accurately, 25 mg of fesoterodine fumarate (purity 98.0%) diluted to volume with methanol, obtaining a concentration of 100 μg mL^{-1} of FESO. The stock solution was stored at 2–8 °C, protected from light and daily diluted to a final concentration of 12 μg mL^{-1} (working solution).

2. 4. Preparation of Sample Solution

To prepare the sample solutions, tablets containing 8 mg of fesoterodine fumarate (6.2 mg fesoterodine base) were accurately weighed and crushed to a fine powder. Appropriate amounts were transferred into individual 50 mL volumetric flasks. After adding 30 mL of methanol, the flasks were vortex mixed for 3 min. The samples were made up to volume with methanol, transferred to appropriate tubes and centrifuged at 3000 × *g* for 10 min. An aliquot of the clear supernatant liquid at final concentration of 100 μg mL^{-1} of the active pharmaceutical ingredient was filtered through a 0.45 μm membrane filter (Millipore Corp). An aliquot of 3 mL of this solution was transferred into a 25 mL volumetric flask and marked up to volume with water in order to produce a final concentration of 12 μg mL^{-1} (working solution).

2. 5. Validation of the 2D-UV Method

Method validation was performed following ICH specifications for specificity, linearity, accuracy, precision, robustness, limit of detection (LD) and quantitation (LQ) (15).

2. 5. 1. Specificity

The evaluation of the specificity of the method was performed by preparing placebo of tablet containing the same excipients of the commercial products. Placebo solutions (12 μg mL^{-1} in theory) were prepared using the same procedure for the sample preparations (n = 3). In a separate study, drug with the same concentration was prepared independently from pure drug stock and analyzed. To maintain an adequate simulation of the presence of excipients in real samples, the concentration for both solutions was the same. All the solutions were scanned from 300 to 200 nm, evaluated by second-derivative spectra and checked for any interference in the absorbance at tested wavelength.

2. 5. 2. Linearity

The analytical curves were obtained with seven concentrations of reference solution in the range of 2–24 μg mL^{-1} (2, 4, 8, 12, 16, 20, and 24 μg mL^{-1}). Each solution was prepared in triplicate. The linearity was evaluated by linear regression analysis by the least-square regression method, which was used to calculate the correlation coefficient, y-intercept and slope of the regression line. The curves were validated by means of the analysis of variance (ANOVA). The separate weighings of synthetic mixtures of the drug product components was also performed during investigation of the range.

2. 5. 3. Precision

The precision was determined by repeatability (intra-day precision) and intermediate precision (inter-day precision). Repeatability was evaluated assaying six de-

terminations at the same concentration (12 μg mL^{-1}), during the same day, under the same experimental conditions. The intermediate precision was studied by comparing the results obtained on three different days. Precision was expressed as relative standard deviation (RSD).

2. 5. 4. Accuracy

This parameter was determined by the recovery test that consisted on adding known amounts of reference solution to the sample solutions (prepared according to sample preparation). Aliquots of 0.5, 1.0, and 1.5 mL of FESO reference solution 100 μg mL^{-1} were transfered to the sample solutions during the last dilution of the samples. The final concentrations of reference substance in each level were: 2, 4, and 6 μg mL^{-1}.

2. 5. 5. LD and LQ

LD/LQ parameters are not a requirement for drug assay; however, it is always useful to demonstrate that the analyses are being conducted in a region which is above the LQ value. The LD and LQ were calculated based on the standard deviation of the response (y-intercepts of regression lines) and the slope using three independent analytical curves, as defined by ICH. LD and LQ were calculated as $3.3\sigma/S$ and $10\sigma/S$, respectively, where σ is the standard deviation of the response and S is the slope of the calibration curve.

2. 5. 6. Robustness

In order to study the simultaneous variation of the factors in the considered responses, a multivariate approach using design of experiments is recommended in robustness testing. A Plackett–Burman design was used to examine the effects of three factors, studied at two levels (high and low): $\Delta\lambda$ (2; 8), scaling factor (80; 120) and different solvents (H_2O:Methanol (1:1); 0.1M HCl) in 12 experiments.[16] The ranges examined were small deviations from the method settings. The response is the percentage of FESO in the commercial tablets (relative to their label claimed concentration) obtained compared to the reference solution in each experiment. All experiments were performed in randomized order to minimize the effects of uncontrolled factors that may introduce a bias into the response. The statistical analyses of the data were performed by the MINITAB 14 (Minitab Inc, State College, PA, USA) data analysis software.

2. 6. FESO Assay in Commercial Tablets

The validated 2D-UV spectrophotometric method was applied for FESO quantitation in extended-release tablets. Moreover, the obtained results were compared statiscally by ANOVA to those obtained using the validated LC, CE, and LC-MS/MS methods.

3. Results and Discussion

3. 1. Method Development

Spectrophotometric technique provides practical and significant economic advantages over other methods. The development of a more convenient, simple, less time-consuming and environmentally friendly spectrophotometric method for routine analysis of FESO in pharmaceutical formulation is highly desirable.

In this work, different solvents were investigated to develop a suitable 2D-UV spectrophotometric method for the analysis of FESO in extended-release tablets. For selection of diluents, the criteria employed were the sensitivity of the method, the easiness of the sample preparation, and the solubility of the drug. Methanol was selected to first step dilution of FESO since it had a great capability to dissolve the drug, mainly during extraction from tablets. However, in order to reduce the use of organic solvent, water was used as final diluent. Water is the better solvent considering toxicological risks and the absence of demanding residue storage, and it presented a good potential to dissolve the drug in conditions assayed. The drug stability study was accomplished for the development and validation of the method. The stability of FESO in water was evaluated to verify if any spontaneous degradation occurs when the samples are prepared. The data obtained showed that sample solutions were stable during up to 48 h at 2–8 °C and for 6 h at room temperature, showing non-significant change (< 2%) relative to freshly prepared samples, as suggested.[17]

Zero-order UV-Vis spectrum of FESO in water showed maximum drug absorption wavelength around 200 nm. However, significant interference from the tablet excipients was verified in all the region of FESO absorption spectrum, which precludes the analytical use of zero-order spectrophotometry (Fig. 2(a)). The first derivative was also discarded due to insufficient selectivity (Fig. 2(b)). For this reason, the 2D-UV method was considered to be ideal for solving the overlapping of excipients absorption over FESO signal. As observed in Figure 2(c), the zero-crossing for tablet 8 mg placebo solution appears at 228 nm. Therefore, this value was selected as optimum to determine FESO in the presence of the pharmaceutical excipients.

Derivative spectra can be used to clarify absorption bands in more complex UV spectra. Compared with conventional spectrophotometric determinations, derivative spectrophotometry has proved to be of a great value in eliminating the interference from excipients,[14] especially when applied to tablets with large amounts of excipients, as Toviaz tablets. It has an approximate drug-excipient ratio of 1:41.

Derivative spectra can be obtained by mathematical methods. The advantages of the mathematical techniques are that derivative spectra may easily be calculated and recalculated with different parameters, and smoot-

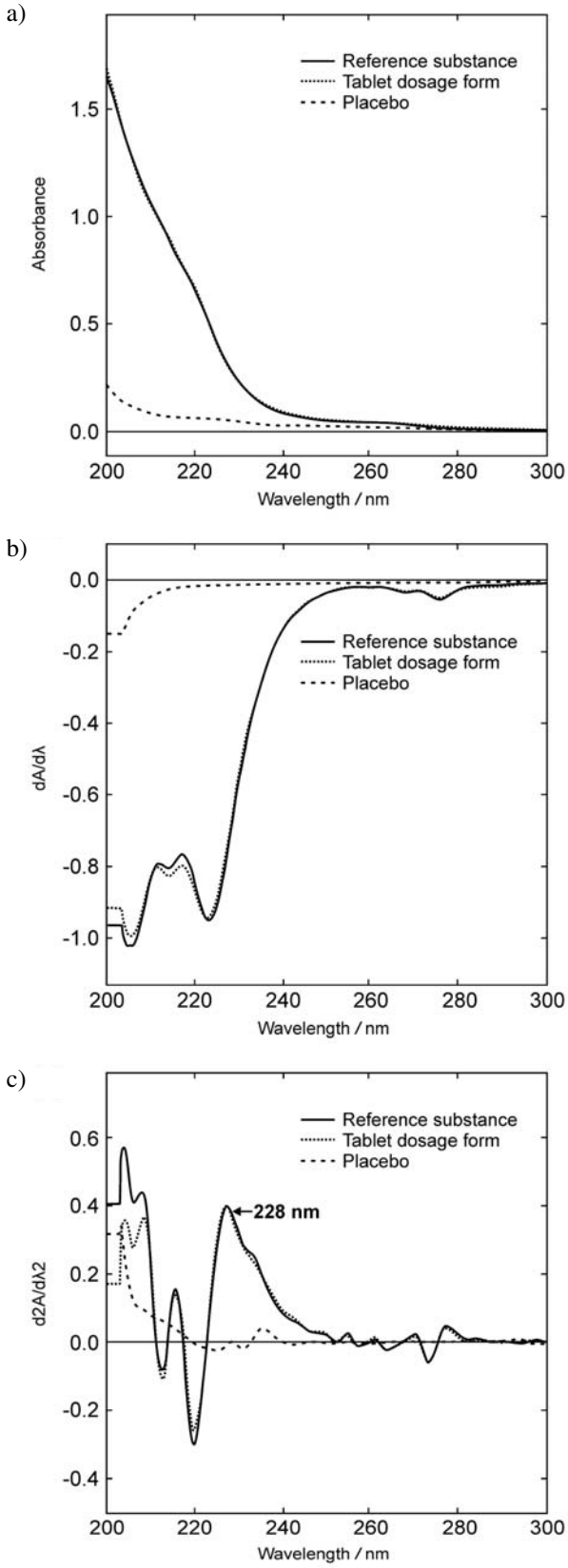

Figure 2. Zero-order absorption spectra (a), first-order derivative spectra (b) and second-order derivative spectra (c) of fesoterodine reference substance solution, sample solution and placebo solution, in water at concentration of 12 μg mL^{-1}.

hing techniques may be used to improve signal-to-noise ratio. To use mathematical techniques, the spectrum is first digitalized with a sampling interval of Δλ, the size of Δλ is dependent upon the natural bandwidth of the bands being processed and of the instrumental bandwidth of the instrument used to generate the data. For the derivatization process, it is important to be able to control the degree of smoothing that is applied in order to adapt to differing analytical problems.[14,18] To verify the optimum Δλ for obtaining second-derivative spectra various values of Δλ were tested, and a Δλ of 4 nm was chosen as the most appropriate in order to give an adequate signal-to-noise ratio. Increasing Δλ, the signal-to-noise ratio improves and the fluctuation in a derivative spectrum decreases. However, if the value of Δλ is too large, the spectral intensity signal of second-derivative deteriorates.[13]

3. 2. Method Validation

3. 2. 1. Specificity

The second-order derivative spectra (Fig. 2(c)) analyses show that formulation excipients of the pharmaceutical tablet products did not interfere in the 2D-UV method at the determination wavelength (228 nm), allowing a reliable determination.

3. 2. 2. Linearity

A linear relationship was found between the absorbance and the concentration of FESO in the range of 2 to 24 μg mL^{-1}. The representative linear equation was $y = 0.0383x + 0.0669$, calculated by the least squares method, and the determination coefficient ($r^2 = 0.9999$) was highly significant. The analytical data were validated by means of ANOVA that demonstrated significant linear regression (f calculated = 42039.47 > f critical = 4.60; $P < 0.05$) and no significant deviation from linearity (f calculated = 0.62 < f critical = 2.96; $P > 0.05$). These results were proven according by successful application of the analytical method to synthetic mixtures of the drug product components to which known amount of analyte added within the range of method.

3. 2. 3. Precision

Precision was determined by studying the intra-day and inter-day precision. The experimental values obtained for the determination of FESO in samples are presented in Table 1. The variability of the results was low with RSD values of less than 1.45% to intra-day precision, and the value of inter-day precision was 1.15% in extended-release tablets. RSD values found for the analytical method were within the acceptable range indicating that this method has excellent repeatability and intermediate precision.

Table 1: Intra-day and inter-day precision data of second-derivative UV spectrophotometric method for fesoterodine in tablet dosage form.

Day	Concentration found[a] (μg mL^{-1})	RSD[b] (%)
1	12.08	1.45
2	12.02	0.79
3	12.13	1.14
Mean[c]	12.08	1.15

[a] Mean of six replicates, [b] RSD, Relative standard deviation, [c] Mean of eighteen replicates

3. 2. 4. Accuracy

The excellent mean percentage recovery values, about to 99%, and their low relative standard deviation values (RSD < 1.0%) were found satisfactory. At each level of the FESO concentration three determinations were performed. The mean recovery was 98.72% (RSD = 0.62%) for extended-release tablets (Table 2). These results revealed that any small change in drug concentration in these solutions could be accurately determined by the proposed analytical method.

Table 2: Experimental values obtained in the recovery test for fesoterodine by using the second-derivative UV spectrophotometric method.

Added Level (μg mL^{-1})	Nominal Concentration (μg mL^{-1})	Mean Concentration found[a] (μg mL^{-1})	Accuracy (%)	RSD[b] (%)
2	14	13.79	98.49	0.62
4	16	15.91	99.41	
6	18	17.68	98.25	

[a] Mean of three replicates, [b] RSD, Relative standard deviation

3. 2. 5. LD and LQ

For calculating the LD and LQ, the calibration equations were generated by using the mean values of the three independent standard curves. The obtained values were 0.38 and 1.27 μg mL^{-1}, respectively.

3. 2. 6. Robustness

The susceptibility of the developed analytical method to changes was tested in order to evaluate the robustness. For this purpose a Plackett–Burman design was employed. The experimental plan and the corresponding responses are summarized in Table 3.

The significance of the effects was evaluated by a Pareto chart of the standardized effects and normal probability plot of the residuals. In Pareto graph (Fig. 3(a)), the ANOVA effect estimates are sorted from the largest absolute value to the smallest absolute value. The magnitude of each effect is represented by a horizontal column. This plot also includes a vertical line to indicate the $P = 0.05$ threshold for statistical significance. Effects in which the bars are smaller than the critical t-value were not considered significant and did not affect the response variables.[19]

Table 3: Selected Plackett–Burman design for the robustness testing of fesoterodine.

Experiment	Δλ	Scaling factor	Solvent	Assay (%)
1	2	80	0.1 mol L^{-1} HCl	100.77
2	2	80	0.1 mol L^{-1} HCl	101.94
3	8	120	0.1 mol L^{-1} HCl	101.96
4	8	80	H_2O:Methanol (1:1)	100.71
5	8	120	0.1 mol L^{-1} HCl	100.04
6	2	120	0.1 mol L^{-1} HCl	103.15
7	2	120	H_2O:Methanol (1:1)	103.01
8	2	120	H_2O:Methanol (1:1)	101.49
9	8	80	0.1 mol L^{-1} HCl	99.94
10	8	80	H_2O:Methanol (1:1)	101.50
11	2	80	H_2O:Methanol (1:1)	102.08
12	8	120	H_2O:Methanol (1:1)	101.76

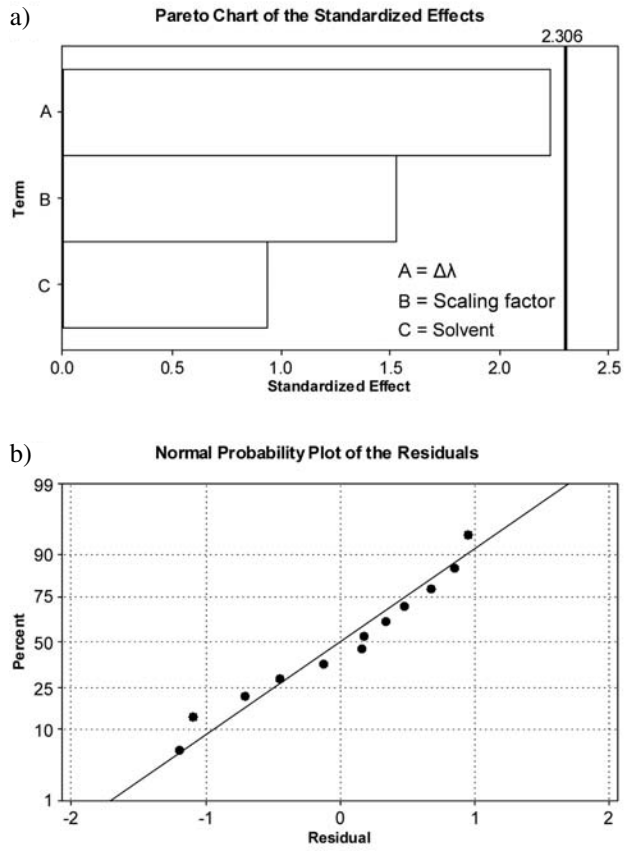

Figure 3. Pareto chart (a) and normal probability plot of the residuals (b) representing the effects of the variables on the fesoterodine assay for the robustness test using the Plackett-Burman design (12 experiments).

The normal probability plot of residuals consists of the difference between the predicted values (as predicted by the current model) and the observed values. Since all values fall onto a straight line it can be concluded that they follow the normal distribution.[19] As observed in Fig. 3(a), the largest magnitude was found in the $\Delta\lambda$ factor, but was not statiscally significant. It indicates that the 2D-UV method is more susceptible to significative changes after some modifications in this factor. Figure 3(b) presents the normal probability plot of residuals for FESO (residual values plotted along the horizontal X-axis; the vertical Y-axis shows the expected normal values for the respective values, after they are rank-ordered). At the studied ranges, the effects of the factors were not statistically significant ($P > 0.05$) for the response studied (assay (%)). Therefore, there were no significant changes in the assay regarding the percentage of FESO contents under the modifications made in the experimental conditions, showing the robustness of the developed method.

3. 3. Analysis of Pharmaceutical Formulations by 2D-UV, LC, CE, and LC-MS/MS Methods

The validated 2D-UV spectrophotometric method was applied for the determination of FESO in tablet dosage forms and the results compared to those obtained using the validated LC, CE, and LC-MS/MS methods, as shown in Table 4. The experimental values of the two methods were compared statistically by ANOVA showing non-significant difference ($P > 0.05$). The proposed method can be useful for the determination of FESO without prior separation of the excipients of the formulation, with the advantage of low use of polluting reagents and very short analysis time. This simpler analytical technique was employed without losing performance, compared to LC, CE, and LC-MS/MS methods, which leads to an affordable method. Since the electrophoretic and chromatographic methods are more expensive, time consuming, and need more steps, the proposed spectrophotometric method is adequate for routine analysis as an alternative technique, simple and cheap.[20]

Table 4: Assay results obtained by 2D-UV, LC, CE, and LC-MS/MS methods for FESO in the pharmaceutical formulation.

	Experimental amount[a]	
Methods	**Assay[b] (%)**	**RSD[c] (%)**
2D-UV	100.21	0.79
LC	99.29	0.68
CE	100.02	0.63
LC-MS/MS	100.67	1.12
P-value ($P > 0.05$)	*f* calculated = 2.87 < *f* critical = 3.10	

[a] Tablets containing 8 mg of fesoterodine fumarate (6.2 mg of fesoterodine base), [b] Mean of five replicates, [c] RSD, Relative standard deviation

4. Conclusions

This work presents an useful, simple and validated a 2D-UVspectrophotometric method for the determination of FESO in pharmaceutical formulations. The method was validated showing satisfactory data for all parameters tested. There is no significant difference between the previously validated LC, CE and LC-MS/MS methods. Thus, it offers advantages over other analytical methods due to its rapidity, simplicity, lower cost, and produces very low levels of dangerous residues promoting benefits to the public health and the environment. Therefore, the proposed method is suitable and can be conveniently used for the routine quality control of FESO in extended-release tablets.

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6. References

1. R. R. Dmochowski, A. Gomelsky, *Curr. Opin. Urol.* **2011**, *21(4)*, 286–290.
2. J. F. Wyman, K. L. Burgio, D. K. Newman, *Int. J. Clin. Pract.* **2009**, *63(8)*, 1177–1191.
3. S. R. Kraus, J. L. Ruiz-Cerdá, D. Martire, J. T. Wang, A. S. Wagg, *Urology* **2010**, *76(6)*, 1350–1357.
4. K. Gupta, K. Kaur, B. S. Aulakh, S. Kaushal, *Curr. Ther. Res.* **2010**, *71(5)*, 273–288.
5. K. McKeage, G. M. Keating, *Drugs* **2009**, *69(6)*, 731–738.
6. M. S. Sangoi, V. Todeschini, M. Steppe, *Talanta* **2011**, *84(4)*, 1068–1079.
7. M. S. Sangoi, M. Steppe, *Eur. J. Mass Spectrom.* **2010**, *16*, 653–661.
8. M. S. Sangoi, V. Todeschini, M. Steppe, *J. AOAC Int. (accepted manuscript).*
9. F. Rojas, C. Ojeda, *Anal. Chim. Acta* **2009**, *635*, 22–44.
10. M. D. Malesuik, C. S. Paim, E. E. S. Schapoval, M. Steppe, *Quim. Nova* **2010**, *33(3)*, 739–742.
11. M. Wrasse-Sangoi, L. T. Secretti, I. F. Diefenbach, C. M. B. Rolim, M. S. Sangoi, *Quim. Nova* **2010**, *33(6)*, 1330–1334.
12. F. A. Siddiqui, A. Z. Mirza, M. H. Zuberi, F. Qureshi, *Med. Chem. Res.* **2011**, *20*, 121–124.
13. R. Bonfilio, M. B. Araújo, H. R. N. Salgado, *J. Braz. Chem. Soc.* **2011**, *22(2)*, 292–299.
14. C. Ojeda, F. Rojas, *Anal. Chim. Acta* **2004**, *518*, 1–24
15. ICH Guideline Q2(R1) on »Validation of Analytical Procedures: Text and Methodology«, International Conference on Harmonization, **2005**, Geneva.
16. G. A. Shabir, W. J. Lough, S. A. Arain, T. K. Bradshaw, *J. Liq. Chromatogr. Rel. Technol.* **2007**, *30*, 311–333.
17. G. A. Shabir, *J. Chromatogr. A*. **2003**, *987*, 57–66.

18. A. Owen, in: A. Townsend (Ed.): Encyclopedia of Analytical Science, Academic Press, San Diego, USA, 1995, pp. 5315–5321.
19. K. Vanaja, R. H. S. Rani, *Clin. Res. Regul. Aff.* **2007**, *24(1)*, 1–23.
20. A. S. L. Mendez, L. Deconto, C. V. Garcia, *Quim. Nova* **2010**, *33(4)*, 981–983.

Povzetek

Pričujoče delo opisuje derivativno UV spektrofotometrično metodo drugega reda za določitev antimuskarinske učinkovine fesoterodina v tabletah s podaljšanim sproščanjem. Metodo smo razvili in zadovoljivo validirali glede na ICH smernice: specifičnost, linearnost, natančnost, točnost in robustnost. Odziv je bil linearen v koncentracijskem območju 2–24 μg mL^{-1} (r^2 = 0,9999, n = 7) pri valovni dolžini 228 nm, ki je bila ničelna presečna točka za raztopine ekscipientov. Meja zaznave ter meja določitve sta bili 0,38 in 1,27 μg mL^{-1}. Natančnost in točnost smo evaluirali z relativnim standardnim odmikom, ki je bil nižji od 2 %. Po evaluaciji s Plackett-Burmanovim načrtovanjem se je metoda izkazala za robustno. Je preprosta, nizkocenovna, porabi se majhna količina okoljsko problematičnih reagentov. Predlagano metodo smo uspešno uporabili za kvantitativno analizo fesoterodina v komercialnih tabletah, rezultate pa smo primerjali z validiranimi metodami s tekočinsko kromatografijo, kapilarno elektroforezo in tekočinsko kromatografijo-tandemsko masno spektrometrijo. Pokazali smo, da gre za statistično nepomembno razliko (P > 0,05).