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Original scientific paper

A rapid and sensitive UPLC–MS/MS method for quantification of erdosteine as bulk drug and in capsules as dosage forms

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Abstract

A rapid, sensitive, specific ultra-performance liquid chromatography-tandem mass spectrometric (UPLC-MS-MS) method was developed for the determination of erdosteine (ERD) in pharmaceutical preparations. The chromatographic separation was achieved with 0.1% formic acid in combination with acetonitrile (25:75 *v/v*) using C_{18} UPLC column, 95Å, 2.1 x 50 mm, 1.8 µm. The flow rate was 0.15 mL/min and the total run time was 2.0 min. The column temperature was kept constant at 40 °C and the injection volume was 5 µL. Ibuprofen was used as internal standard (IS). The mass transitions of ERD and IS were m/z 249.9 → 231.8 and 205.1 → 161.0. Also, another product ion of ERD (m/z 249.80 → 231.80) was monitored as predictive ion during the analysis. The standard calibration curve shows determination coefficient (R^2) greater than 0.996 with a range of 1-5000 ng/mL using the linear regression model. Within-run precision and between-run repeatability were expressed as relative standard deviation and were lower than 5%. The developed method was successfully applied in the analysis of ERD-containing capsule formulation indicating that the method could be used for routine quality control analyses.

Keywords: erdosteine, UPLC-MS/MS, multiple reaction monitoring, pharmaceutical analysis, method validation

Introduction

Erdosteine (ERD), (±)-{[2-oxo-2[(tetrahydro-2-oxo-3-thi-enyl)amino]ethyl]thio} acetic acid, is a mucolytic drug substances that is chemically a thiol derivative characterized by the presence of two thiol groups (Dal Negro, 2008; Moretti and Marchioni, 2007). The thiol groups contain two sulfur atoms, one of which is present in the aliphatic side chain and the other enclosed in the heterocyclic ring. These enclosed sulfhydryl groups have reducing potential and become available for pharmacological activity after hepatic metabolization and opening of the thiolactone ring. Thus, it produces active metabolite M1 (Met 1) or (±)-N-(2-carboxymethylthioacetyl)homocysteine), which contains a –SH group that have mucolytic and antioxidant activity (Braga et al., 2000; Cazzola et al., 2020; Moretti and Marchioni, 2007).

Like the other thiol-based drugs, ERD mainly used for the treatment of a range of respiratory diseases including chronic obstructive pulmonary disease (COPD). It exhibits a versatile pharmacological profile that may positively effect in more than one of the pathological processes occurring in all respiratory disorders characterized by thickened or chronic inflammation, increased mucus production, and increased oxidative stress (Cazzola et al., 2020; Moretti, 2009). Besides, an

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important feature of the pharmacological profile of ERD is improving the efficacy of antibiotic treatment by reducing bacterial adhesion to the respiratory epithelial cell surface (Miyake et al., 1999; Moretti, 2007).

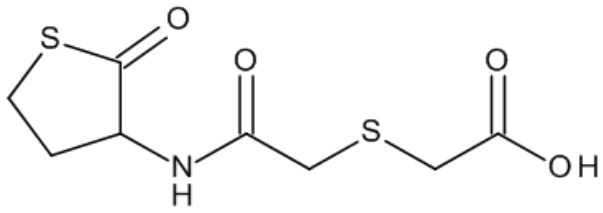

Fig. 1. Chemical structure of erdosteine.

As a natural consequence of its pharmacological importance and being a medicament widely used, various methods have been reported previously to carry out the development of more efficient analytical techniques, destined to analysis of ERD. HPLC-based analysis are the most studied techniques for determination of ERD in pharmaceutical preparations (Kim et al., 2010; Moustafa et al., 2014) and blood serum/plasma samples (Hui Liu et al., 2007; Muramatsu et al., 1998). High-performance thin layer chromatographic (HPTLC) (Mhaske and Dhaneshwar, 2007) and spectrophotometric (Mahrouse et al., 2020; Nanda et al., 2009) methods have also been described. Also, HPLC coupled with tandem mass spectrometry methods have been developed for the determination of ERD in human (Kim et al., 2004) and dog (Dan et al., 2007) plasma samples.

As an improved derivative of HPLC systems, ultra-high performance liquid chromatography (UPLC) has high-quality small porous packing material and a capability of very high pressures. Higher pressure capability and smaller particles in the stationary phase allow the obtaining of an increased efficiency and sensitivity owing to sharper and higher peaks, and also faster chromatographic analysis. Thus, the main advantages of UPLC systems are improving resolution and particularly a significant reduction of analysis time (Gumustas et al., 2013; Mensch et al., 2007; Nováková et al., 2006). In a recent study, Bertolini et al. (2018) have been reported an UPLC-PDA-QTOF-MS assay method for ERD in effervescent tablets. However, the reported method mainly focused on the known impurities and new degradation products with ERD, therefore, the total analysis time of the method is 17 min. which can be considered as quite long for routine quality control analysis of single pharmaceutical substance.

The objective of this study was to develop a rapid and sensitive ultra-performance liquid chromatography-tandem mass spectrometer (UPLC-MS/MS) method for the determination of ERD in pharmaceutical preparations. Ibuprofen was used as internal standard (IS). After selective chromatographic separation of ERD and IS, the molecules were detected by multiple reaction monitoring (MRM) mode in triple quadrupole mass spectrometer. MRM mode enables the ability to detect a specific precursor ion, to select that ion for collision-induced fragmentation and, thus, to detect a specific product ion following fragmentation (Kitteringham et al., 2009). Thus, monitoring of product ions was greatly increased specificity of detection and identification of ERD and IS, and optimization of chromatographic separation was simplified. After validation studies, the developed method was successfully applied in the analysis of ERD-containing capsule dosage forms.

Materials and methods

Materials and reagents

ERD with percentage purity of >99% and ibuprofen (purity>99%) were supplied by Novagenix Company (Ankara, Turkey). Acetonitrile and methanol hyper grade for LC-MS systems and formic acid were purchased from Merck (Darmstadt, Germany). Deionized water was prepared daily using Synergy® UV Water Purification System (Merck Millipore, Darmstadt, Germany). ERD-contained capsule formulations were purchased were obtained from Turkish pharmaceutical market.

Instrumentation and Operation Conditions

We conducted the samples analysis using an ultra-performance liquid chromatography system (UHPLC, 1290 Series, Agilent Technologies, Santa Clara, CA, USA) coupled to an Agilent 6490 Triple Quadrupole mass spectrometer (Agilent Technologies), which possessed the triple quadrupole mass spectrometer, a degasser, an autosampler, a column compartment and a binary pump. Chromatographic separation was achieved using a reserved-phase C_{18} UPLC column (ZORBAX RRHD Eclipse Plus C18, 95Å, 2.1 x 50 mm, 1.8 µm, Agilent Technologies, Loveland, CO, USA) maintained at 40 °C, and the autosampler tray temperature was maintained at 10 °C. Separation was achieved by using an isocratic elution with the mobile phase consisting of 0.1% formic acid solution and acetonitrile (25:75, *v/v*). The mobile phase was filtered with 0.45 µm Millipore membrane filter prior to use. The flow rate was 0.15 mL/min and the total run time was 2.0 min. The column temperature was kept constant at 40 °C and the injection volume was 5 µL.

The mass spectrometer was used equipped with a Jet Stream electrospray ion source interface in both negative and positive ionization mode in the mass range of 50–250 Da. Nitrogen was used as the desolvation gas (1000 L h^{-1}) and cone gas (50 L h^{-1}). Ion monitoring conditions were defined as capillary voltage of 2.0 kV, source temperature of 250 °C, and nebulizer pressure 35 psi. Multiple reaction monitoring (MRM) modes of m/z 249.80 → 231.80 for

ERD and m/z 205.1 → 160.80 for IS were utilized to conduct quantitative analysis. Also m/z 249.80→ 203.80 product ion was also monitored as predictive ion for ERD. Further information about the MRM conditions were shown in Table 1.

Preparation of standards and quality control (QC) samples

The stock solutions of ERD (1.0 mg/mL) and IS (1.0 mg/mL) were prepared in methanol. The working standard solutions of ERD and IS was prepared from those stock solutions by dilution with methanol. Further dilutions of working solutions for calibration and controls were prepared from stock solutions using methanol by the same way. Working solutions were stored at -20 °C and were brought to room temperature before use. The quality control solutions were prepared daily.

Method Validation

Validation studies was carried out according to the ICH Q2(R1) guideline to confirm the analytical performance of the method (Borman and Elder, 2017).

Selectivity and specificity

Chromatograms of blank solutions and ERD containing samples were compared. All samples were examined for interferences that could be observed during the same retention time of ERD and IS. For selectivity, samples were prepared from capsule formulations and analyzed to determine whether there are any interferences caused by endogenous matrix components in selected mass transitions (Ermer and Miller, 2006) (Fig. 3).

Linearity and sensitivity

In order to generate a calibration graph in the range of 5–5000 ng/mL, standard working solutions at seven different concentrations of ERD and IS (250 ng/mL) were prepared triplicate. These samples were analyzed using developed method and least-squares weighted (1/x2) linear regression analysis was applied and the equation was formed. In sensitivity studies, continuous lower accumulations of standard solution were analyzed. According to ICH recommendation, the detection and quantification limits were calculated based on the signal-to-noise ratio of 3:1 and 10:1, respectively (ICH, 2005).

Precision and accuracy

Intra- and inter-day precision of the method were determined by analyzing quality control samples (QC's) corresponding to low, medium and high concentration within the calibration curve (2.5, 250 and 2500 ng/mL). For determining intraday precision, QC samples were analyzed three times in a day. Inter-day precision was determined by analyzing the freshly prepared QC samples in three days in a row. The relative standard deviations were used to determine the precision of the method. To evaluate the accuracy of the method, recovery values were used after the determination of ERD at three concentration levels: 400, 500, and 600 ng/mL (corresponding to 80, 100, and 120% of the working concentration). Triplicate samples at each level were analyzed. The recovery was calculated with the detected amount versus the added amount (ICH, 2005).

Analysis of Pharmaceuticals and Recovery

The applicability of the methods for the determination of ERD in solid dosage forms (capsules) was examined by analyzing two marketed medicinal products of ERD - Erdostin 300 mg (Sandoz Pharmaceuticals Inc.) and Evosten 300 mg (Abdi Ibrahim Pharmaceuticals Inc). Each drug contents were removed and weighed, separately. Equivalent amount to one capsule was weighed and dissolved in methanol. The solutions were sonicated for 15 min to complete dissolution. After filtered through a microfilter, the solutions were diluted with an appropriate concentration (250 and 500 ng/mL) and transferred to an autosampler vial. 5 μL was injected into the UPLC-MS/MS system for analysis. Average recoveries were calculated by comparing the measured concentration to nominal concentration.

Results and Discussion

Optimization of UPLC–MS/MS conditions

The optimum mass spectrometric parameters were determined by testing different conditions to obtain the maximum abundances of product and fragment ions. ERD and IS solutions at 1000 ng/mL were injected into the mass spectrometer by direct infusion, and full scan mass spectra were obtained in both positive and negative ionization modes using ESI source in the mass range of 80–300 Da. The optimum peak intensity for ERD was obtained in the negative ion mode whereas IS was much intense in negative mode. Then, the MRM mode was used in order to determine the two most specific and/or intense product ions for each precursor ion. MRM is a powerful method of targeted mass spectrometry that can be used to selectively detect the specific molecules based on the screening of selected precursor molecule-to-fragment ion transitions (Sherwood et al., 2009). The transitions from precursor to product were found as m/z 249.8 → 231.8 for ERD, 205.1 → 161.8 for IS. Besides, a predictive ion, m/z 249.8 → 203.8 for ERD was also monitored for making method more specific. For IS, however, only one product ion was present and there was no additional fragmentation product that could be selected as the predictive ion (Fig. 2). The optimum collision energies were found as 2 and 1 eV, for ERD and IS, respectively. Further details about the optimum mass spectrometric conditions were shown in Table 1.

The mobile phase was optimized by testing of different solvents, ratios and flow programs in order to achieve good separation with a good resolution of ERD and IS peaks within a short analysis time. Shalaan et al. have previously stated that high concentration of acetonitrile in mobile phase was an important factor that led to the elution of IS in a reasonable retention time with acceptable peak asymmetry (Hyoscine, 2013). We observed that the apolar character of IS became more dominant during the chromatographic separation, causing it to hold into the C_{18} column and acetonitrile should be used for its elution. It was also found that acidic aqueous solutions possessed a significant improvement on the resolutions of ERD and minimized peak tailing, comparing with other solvent. Thus, the optimal mobile phase, consisting of water (0.1% formic acid) and acetonitrile, was finally employed with a flow of 0.15 mL/min. Under these specified conditions, the retention times of ERD and IS were about 1.017 and 1.554 for ERD and IS, respectively. Total analysis time was 2.0 min. which is significantly faster runtime than previous studies (Bertolini et al., 2018; Heying Liu et al., 2021; Ma et al., 2012; Onal and Kepekci Tekkeli, 2020) (Fig. 3).

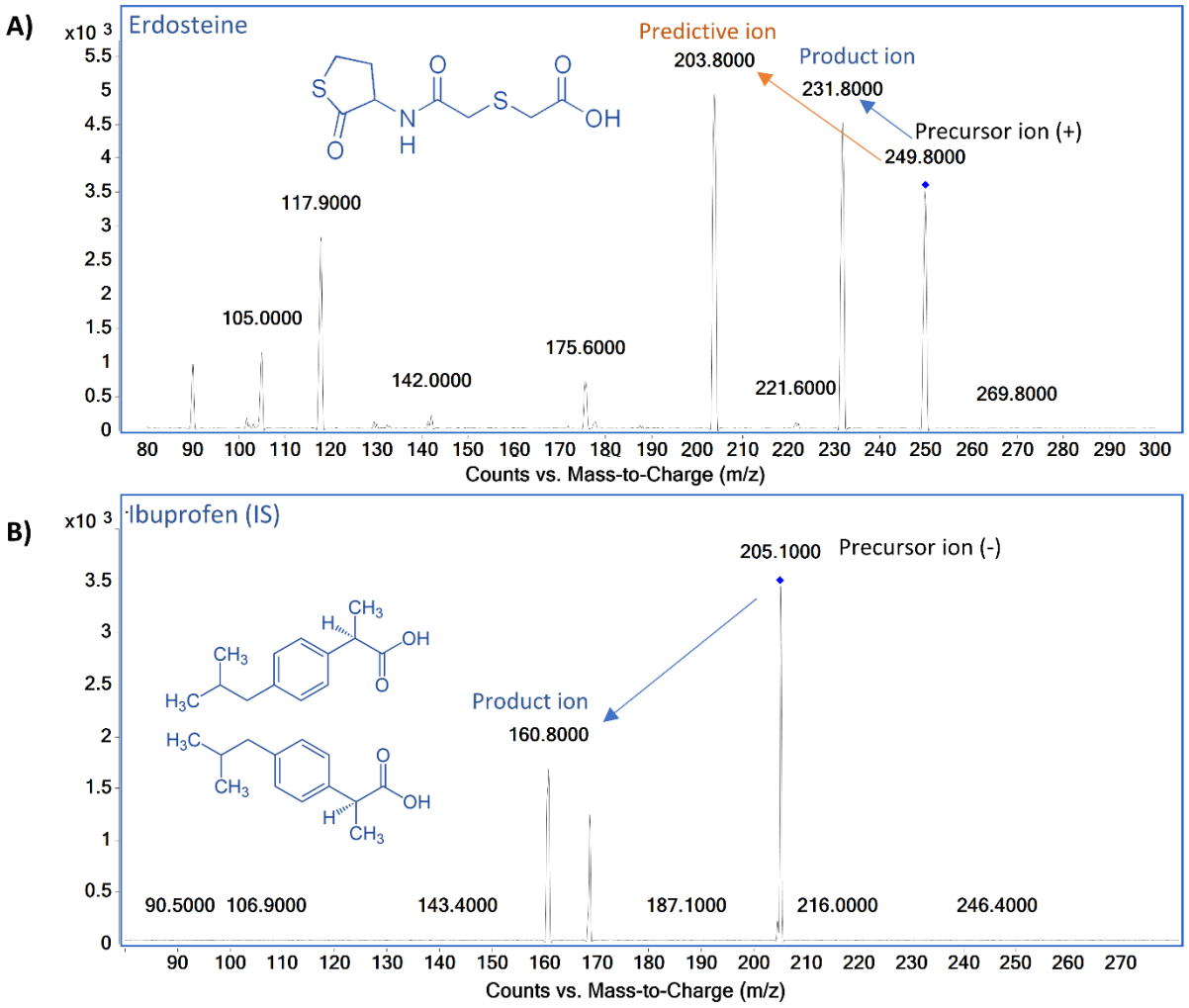

Fig. 2. Product ion mass spectra for (A) Erdosteine (m/z 249.8 → 231.8), (B) IS (Ibuprofen) (m/z 205.1 → 160.8).

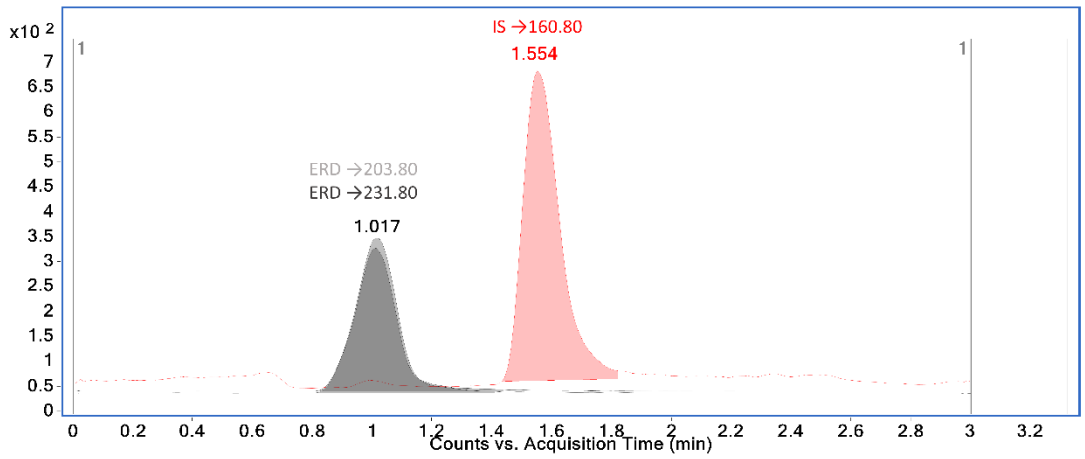

Fig. 3. UPLC-MS/MS total ion current (TIC) chromatogram of ERD (250 ng/mL) and IS (1000 ng/mL). (ERD (MRM: 249.8 → 230.80 Product and 249.8 → 203.8 Predictive ion) and Ibuprofen (internal standard, MRM: 205.1 → 160.8).

Selectivity and specificity

The representative MRM chromatograms of solutions obtained from capsule formulations (250 and 500 ng/mL) were shown in Fig. 4. It indicated that good separation was obtained both standard and real sample conditions and no interfering peaks were found at the retention time of ERD and IS.

Linearity and Sensitivity

The calibration curves were constructed by plotting peak-area ratio of ERD to IS versus concentrations. The calibration curve was constructed by analyzing at seven different concentrations of ERD and the developed method was linear in the range of 1- 5000 ng/mL with a coefficient of determination (R^2) was higher than 0.996 (Fig. 4). LOD was calculated by injecting continuous lower accumulation of standard solutions using the developed method and it was observed as 0.1 ng/mL and S/N value was 4. The LOQ corresponding to S/N ratio of 10:1 was found to be 1 ng/mL, which shows the adequate sensitivity of the method. The calibration curves of the method have provided a wide concentration range (1–5000 ng/mL) with an acceptable repeatability compared to the previous studies (Kim et al., 2010; Heying Liu et al., 2021; Mahrouse et al., 2020).

Table 1. Optimized MS/MS parameters of the method

	Erdosteine (Product Ion)	Erdosteine (Predictive Ion)	IS (Product Ion)
Ionization Mode	ESI+Agilent Jet Stream		
MRM Transitions (m/z)	249.80 → 231.80	249.80→ 203.80	205.1 → 160.80
Fragmentor Voltage (V)	23	23	60
Collision Energy (V)	2	8	1
Polarity	Positive	Positive	Negative
Dwell Time	165	165	165
Gas Temp (°C)	250	250	250
Gas Flow (l/min)	8	8	8
Nebulizer (psi)	35	35	35
SheathGasHeater	250	250	250
SheathGasFlow	10	10	10
Capillary (V)	2000	2000	2000

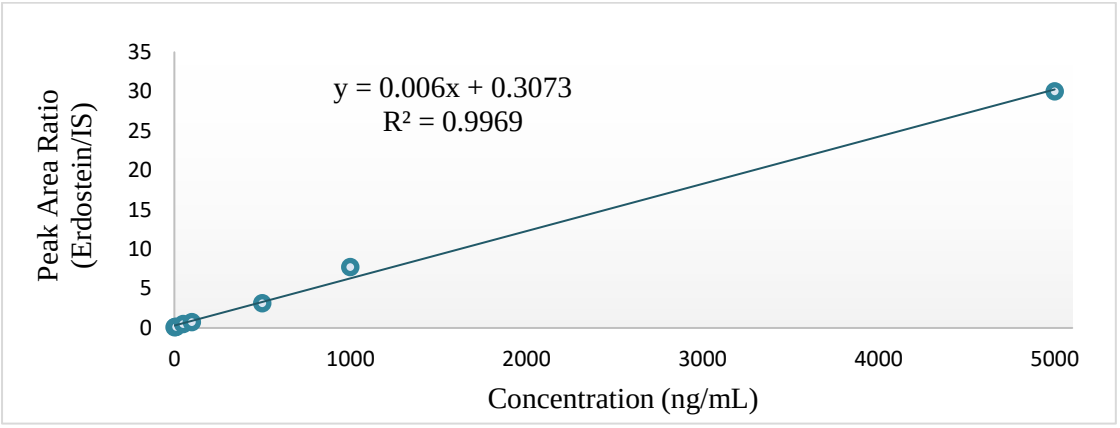

Fig. 4. The calibration curve of the method obtained from linear regression analysis of the method (n=6).

Precision and accuracy

The RSD values for method precision obtained from the determination of QC solutions at three concentration levels were less than 5%, confirming the repeatability of the method. Intra-day precision was examined with the mixture standard solutions during a single day, while the inter-day precision was determined over three consecutive days. The results are indicated that there is no significant difference in the intra-day and inter-day measurements (Table 2). The outputs of the accuracy studies were shown in Table 3. The accuracy of the method was determined by comparing the measured mean concentrations and added concentrations at the three concentration level of ERD (corresponding to 80%, 100% and 120% of standard working solution). Mean recoveries for ERD were 98.2% ($P_{95\%}$= ± 4.0%), 102.4% ($P_{95\%}$= ± 2.6%) and 97.8% ($P_{95\%}$= ± 1.4%) at 80%, 100% and 120% of the working concentration, respectively. Obtained results indicate that the method is suitable for routine analysis of ERD in capsule formulation within 95-105% specification limits.

Table 2. Results obtained from testing of the accuracy of the method

Spiked Level % (n=3)	Amount Added (ng/mL)	Amount Recovered (ng/mL)	Recovery %	RSD %	*P*, 95% confidence interval
80	400	392.60	98.2	3.72	98.2 ± 4.0 %
100	500	511.75	102.4	2.29	102.4 ± 2.6 %
120	600	586.50	97.8	1.20	97.8 ± 1.4 %

Table 3. Precision of the developed method (n=6). x̄: Mean of the six replicated analysis, SD: Standard deviation, RSD: Relative Standard deviation

	Intra-day		Inter-day	
Added (ng/mL)	Found x̄ (ng/mL) ± SD	Precision RSD %	Found x̄ (ng/mL) ± SD	Precision RSD %
2.5	2.48 ± 0.12	4.83	2.47 ± 0.09	3.64
250	253.82 ± 11.61	4.57	259.40 ± 10.26	3.95
2500	2490.3 ± 32.56	1.31	2502.72 ± 18.80	0.75

Table 4. The assay results and recovery of pharmaceuticals containing ERD in two different concentration levels (n=6)

	Erdostin 300 mg ERD		Evosten 300 mg ERD	
	250 ng/mL	500 ng/mL	250 ng/mL	500 ng/mL
$\bar{x}$ (ng/mL) ± SE	256 ± 9.12	515.30 ± 16.54	249.20 ± 15.55	510.65 ± 12.50
SD	5.26	13.56	6.78	8.78
RSD %	2.05	2.63	2.72	1.48
Average Recovery %	102.40	103.06	99.68	102.13

Analysis of pharmaceuticals and recovery

In order to assess the applicability of the UPLC-MS/MS method, the determination of ERD was performed in its capsule formulations (Fig. 5). Experimental results of the amount of ERD in the selected commercial pharmaceuticals were in good agreement with the ERD content of these formulations. The drug content was found to be between 99.68% and 102.13% for ERD six different lots of each drug (Table 4). These results suggest that the method can be used in routine analysis of ERD-containing capsule formulations.

Conclusion

In this study, rapid and sensitive UPLC-MS/MS method was developed for the accurate determination of ERD in bulk and tablet dosage form. The main advantages of this method are shorter run time, wide working range and sensitivity. As this method has the lowest analysis time is more rapid than the other published mass spectrometry based ERD analysis methods. After validation studies, the developed method was successfully applied in the analysis of ERD-containing tablet formulation indicating that the method could be used for routine quality control analyses.

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Conflict of interest

All authors declare no conflict of interest.

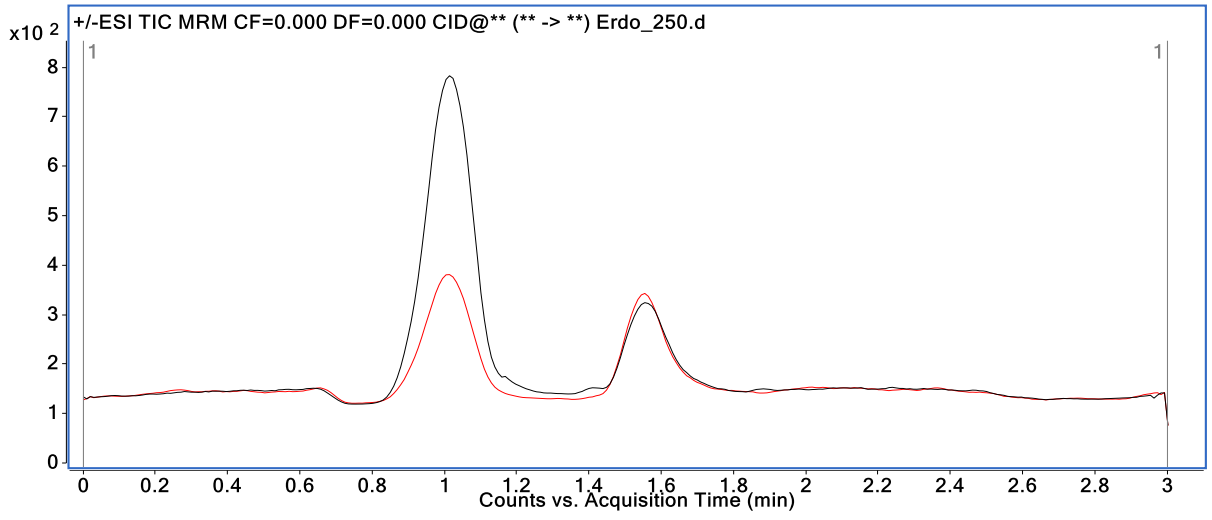

Fig. 5. A representative UPLC-MS/MS chromatogram of ERD (250 and 500 ng/mL) solutions prepared from capsule formulations.

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Резиме

Брз и сензитивен UPLC–MS/MS метод за квантификација на ердостеин како балк супстанција и во капсули како дозирани форми

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Брза, сензитивна, специфична течна хроматографска метода со масена спектроскопија (UPLC-MS-MS) е развиена за определување на ердостеин (ERD) во фармацевтски препарати. Хроматографското раздвојување беше постигнато со 0,1% мравја киселина во комбинација со ацетонитрил (25:75 *v/v*) со користење на C18 UPLC колона, 95Å, 2,1 x 50 mm, 1,8 µm. Брзината на проток беше 0,15 mL/min, а времето на анализата беше 2,0 мин. Температурата на колоната се одржуваше константна на 40 °C, а волуменот на инјектирање беше 5 µL. Ибупрофен се користеше како внатрешен стандард (IS). Масовните транзиции на ERD и IS беа m/z 249,9 → 231,8 и 205,1 → 161,0. Исто така, друг поттикнувач на јони на ERD (m/z 249,80 → 231,80) беше следен како маркер јон за време на анализата. Стандардната крива на калибрација покажа коефициент на корелација (R^2) поголем од 0,996 со опсег од 1-5000 ng/mL, користејќи го моделот на линеарна регресија. Прецизноста и повторливоста помеѓу анализите беа изразени како релативно стандардно отстапување и беа пониски од 5%. Развиениот метод беше успешно применет и за анализата на капсула што содржи ERD, што укажува на фактот дека методот може да се користи за рутинска контрола на квалитетот на анализите.