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Stability-indicating micellar electrokinetic chromatography method for the analysis of sumatriptan succinate in pharmaceutical formulations

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ABSTRACT

A micellar electrokinetic chromatography method for the determination of sumatriptan succinate in pharmaceutical formulations was developed. The effects of several factors such as pH, surfactant and buffer concentration, applied voltage, capillary temperature, and injection time were investigated. Separation took about 5 min using phenobarbital as internal standard. The separation was carried out in reversed polarity mode at 20 °C, 26 kV and using hydrodynamic injection for 10 s. Separation was achieved using a bare fused-silica capillary 50 μm × 40 cm and background electrolyte of 25 mM sodium dihydrogen phosphate—adjusted with concentrated phosphoric acid to pH 2.2, containing 125 mM sodium dodecyl sulfate and detection was at 226 nm. The method was validated with respect to linearity, limits of detection and quantification, accuracy, precision and selectivity. The calibration curve was linear over the range of 100–2000 μg mL^{-1}. The relative standard deviations of intra-day and inter-day precision for migration time, peak area, corrected peak area, ratio of corrected peak area and ratio of peak area were less than 0.68, 3.48, 3.28, 2.97 and 2.83% and 2.01, 5.50, 4.46, 4.92 and 4.07%, respectively. The proposed method was successfully applied to the determinations of the analyte in tablet. Forced degradation studies were conducted by introducing a sample of sumatriptan succinate standard solution to different forced degradation conditions using neutral (water), basic (0.1 M NaOH), acidic (0.1 M HCl), oxidative (10% H_2O_2) and photolytic (exposure to UV light at 254 nm for 2 h). It is concluded that the stability-indicating method for sumatriptan succinate can be used for the analysis of the drug in various samples.

1. Introduction

Sumatriptan succinate (SS), 3-[2-(dimethylamino)ethyl]-*N*-methyl-1H-indole-5-ethanesulfonamide succinate (Fig. 1) is a 5-hydroxytryptamine (5-HT1B/1D) receptor agonist used in the treatment of migraine headache [1,2]. The mechanism of action of the (5-HT1B/1D) receptor agonist has been studied and leads to two main theories. The first theory is that SS acts as a vasoconstrictor of dilated intracranial blood vessels. Another possible mode of action is that it behaves as an inhibitor of the pro-inflammatory neuropeptide release which leads to headache relief [3].

Stability indicating methods for drugs are established and studied in order to provide evidence on the quality of bulk drug when exposed to external environmental conditions such as pH, temperature, and light. The data obtained from these studies facilitate storage conditions; re-test periods as well as shelf lives to be established. On the other hand, stress testing allows the determination of the inherent stability of the molecule when subjected to adverse conditions by establishing the degradation pathways which is analogous to the established metabolic profile [4].

Several methods have been reported for the analytical determination of SS in plasma and pharmaceutical formulations using high performance liquid chromatography (HPLC) with UV [1,2,5], or fluorescence [3], mass spectrometry [4,6–9], electrochemical [10], densometric, or spectrophotometric detection [11], High performance thin layer chromatography (HPTLC) [12], capillary electrophoresis (CE) [13] and voltammetry [14] have also been reported.

CE is a powerful analytical technique that is carried out in narrow-bore capillaries under the influence of an external electric field [15,16]. CE has great impact in the drug discovery due to its unique separation mechanism, speed of analysis, versatility and also its high efficiency [17]. Moreover, CE has shown great potential in the analysis of inorganic ions, biopolymers as well as drugs.

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Micellar electrokinetic chromatography (MEKC) is one of the modes in CE that has growing interest in drug analysis due to its ability to separate neutral analytes as well as charged ones [18]. Under neutral or basic conditions, the bulk solution migrates toward the cathode by the electroosmotic flow (EOF) once the voltage is applied, whereas the micelle is forced toward the anode by the electrophoresis effects. Usually the EOF is stronger than the electrophoretic migration of the sodium dodecyl sulfate (SDS) micelle, and therefore, the micelle migrates toward the cathodic side at slower velocity than the aqueous phase. Neutral analyte which is introduced to the micellar solution at the anodic side will distribute between the micelle and the aqueous phase. Analyte that is completely incorporated into the micelle will migrate toward the cathode at the lowest or the same velocity as the micelle, whereas non incorporated analytes will migrate at the same velocity as the EOF toward the cathode. Depending on the distribution coefficients between the micellar and the aqueous phase, analytes will be detected in an increasing order of hydrophobicity at the cathodic side [19].

To the best of our knowledge, there is no analytical method reported for the determination of SS drug using MEKC. Therefore, the main objective of the current work was to develop a MEKC method, systematically optimized and validated in light of the ICH guidelines [20], for the stability indicating capabilities of SS. The developed method will be applied to the determination of SS under different stressed conditions in addition to the analysis of pharmaceutical tablets.

2. Experimental

2.1. Chemicals and reagents

SS and phenobarbital (IS) standards were kindly donated by HIKMA Pharmaceutical Company, Amman, Jordan. Sodium hydroxide, sodium dihydrogen phosphate anhydrous, sodium dodecyl sulfate and phosphoric acid (85%) were purchased from Sigma–Aldrich (St Louis, USA). Hydrogen peroxide (31%) and hydrochloric acid (37%) were purchased from Merck (Darmstadt, Germany). Commercial pharmaceutical preparation in the form of tablets was purchased from local pharmacies. Deionized water was produced using a Milli-Q system (Millipore, Bedford, USA), and was used throughout for the preparation of solutions.

2.2. Instrumentation and electrophoretic conditions

Separations were conducted on a HP^{3D}CE capillary zone electrophoresis system (Agilent Technologies, model G1600A, Waldbronn, Germany). The unit was equipped with photodiode array (PDA) detector. Uncoated fused-silica capillary of 48.5 cm total length (effective length to detector 40 cm) and 50 μm internal diameter from Agilent Technologies was used. Data acquisition was performed with ChemStation Software. The new capillary was conditioned by flushing for 30 min with 1 M NaOH, 10 min with 0.1 M NaOH and 15 min with water. Between injections, it was preconditioned with 0.1 M NaOH, and then purified water, followed by the background electrolyte (BGE), each for 3 min between the runs. Samples and standards were injected hydrodynamically at 50 mbar for 10 s under the following conditions: voltage, 26 kV (reversed polarity); capillary temperature, 20 °C; detector wavelength, 226 nm; and BGE, 25 mM sodium dihydrogen phosphate anhydrous - adjusted with phosphoric acid (85%); pH, 2.20 containing SDS, 125 mM. At the end of the day, a final 5 min washing with water was performed. All standards, sample solutions, BGE and NaOH solution were filtered through 0.2 μm regenerated cellulose membrane filter (Germany) using an Agilent solvent filtration kit. An Orion pH meter model EA 940 (Orion Research, Cambridge, USA) was used for pH measurements, while analytical balance model AY 220 (Shimadzu Corp., Japan), ultrasonic water bath sonicator model 28X (ULTRAsonik, Ney Dental, Yucaipa, California), and UV irradiator model USHIO Optical Modulex, America Inc. (Cerritos, Ave, Cyres, California) were also used.

2.3. Preparation of standard and pharmaceutical sample solutions

Stock solutions of SS (2500 μg mL^{-1}) and phenobarbital (500 μg mL^{-1}) as internal standard were prepared in water. The stock solutions were used to prepare calibration standards. Working solutions were prepared by serially diluting the stock solution with water after spiking with the internal standard to a final concentration of 100 μg mL^{-1}. All solutions were kept in the refrigerator when not in use.

Imigran tablets containing 50 mg of SS were accurately weighed, ground and mixed in a mortar to fine powder. Accurately weighed amount of the powder equivalent to 25 mg of SS was taken and dissolved by adding water, sonicated using ultrasonic water bath for 5 min and then diluted to 25 mL with water after spiking with the phenobarbital internal standard to a final concentration of 100 μg mL^{-1}. The sample was filtered through a regenerated cellulose membrane (0.2 μm). This solution was introduced to the CE system for the separation.

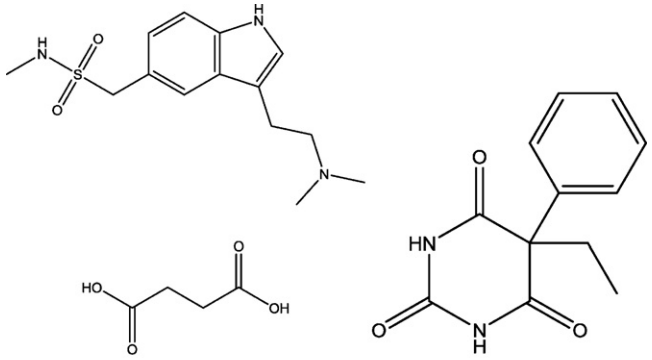
2.4. Forced degradation studies

Selectivity and forced degradation studies were conducted according to the ICH guidelines [20] by introducing a sample of SS standard solution to different forced degradation conditions using neutral (water), basic (0.1 M NaOH), acidic (0.1 M HCl), oxidative (10% H_2O_2) and photolytic (exposure to UV light at 254 nm for 2 h). The neutral, acidic, basic and oxidative solutions were refluxed at 80 °C for 6 h and sampled at 2 h intervals. To check the peak purity of SS in the generated electropherograms, a photodiode array detector was used. Interferences from the tablet were assessed by preparing tablet placebo according to the manufacturer's practice. Imigran SS tablet placebo tablet consisted of microcrystalline cellulose, croscarmellose sodium, lactose, methylhydroxypropyl cellulose, triacetin, titanium dioxide, magnesium stearate, iron oxide, calcium hydrogen phosphate anhydrous and sodium hydrogen carbonate [1,21]. Excipients were examined for their potential interferences with the SS peak. The placebo concentration in the synthetic samples was fixed at 6.0 mg mL^{-1} and then subjected to the CE analysis under the same conditions.

3. Results and discussion

MEKC is an interesting analytical technique that is capable of separating neutral and charged analytes that have similar electrophoretic mobilities, and thus can be used for impurity profiling. Other advantages of the MEKC include high separation efficiency, very low chemical consumption and user-friendly operation [22,23].

Preliminary studies in the separation of SS using CZE showed a broad peak (CZE conditions: BGE, 25 mM sodium dihydrogen phosphate—adjusted with concentrated phosphoric acid; temperature, 25 °C; and applied voltage, 24 kV, normal polarity; injection time, 15 s, SS concentration, 500 μg mL^{-1}.). Thus extra attention has been focussed on the BGE composition. Due to the different species in the BGE, thus different migration velocities from one another are expected. Once the voltage is applied, each species will migrate toward the electrode of opposite charge. The velocities of the migrating species depend not only on the electric field, but



Sumatriptan Succinate (SS)

(pK_a 9.63; log K_{ow}, 0.65 [1])

Phenobarbital (IS)

Fig. 1. Chemical structures of drug and phenobarbital (IS) used in the study.

also on the shapes of the species and their environment [24]. The poor peak shape (distorted with severe tailing) obtained (Fig. 2) is attributed to the electromigration dispersion effects which resulted from the conductivity differences between the analyte zones and the BGE. Different BGE compositions have been examined such as citrate and tris, but all of these attempts failed to produce acceptable peak shape.

Since degradation in NaOH produced other peaks as degradants, therefore it was employed for further optimization of the method. The first step in the method development was to choose a suitable BGE. The use MEKC resulted in improvement not only in the peak shape, but also in the separation of the degradants that resulted from the NaOH stress conditions (Fig. 3).

3.1. Optimization of separation conditions

3.1.1. Effect of buffer pH

pH is a very important parameter in the analysis of ionic species in MEKC. Moreover it effects the ionization of the silanol group of the capillary wall, which in turn affects the magnitude of the EOF. SS is a basic drug with pK_a value of 9.63 [1]. At low pH, the amine group becomes protonated, SS molecule will exist predominantly in the positively charged form and will form an ion pair with SDS and thus it will migrate toward the cathode side [25,26]. Reductions in EOF will occur when keeping the BGE at low pH values; therefore, reversed polarity is needed in order to enable migration of the micelles toward the anodic detector. Under the experimental conditions, the positively charged analyte migrated toward the incoming zone of SDS micelles. At the boundary of these zones, the analyte was incorporated into the negatively charged micelles and migrated in reversed polarity toward the detector [27]. In this study, the effect of buffer pH over the range 2.1–2.6 on the migration time using sodium dihydrogen phosphate (adjusted with concentrated phosphoric acid), containing 200 mM SDS concentration was examined. pH 2.2 was chosen since peaks with good shape and reasonable migration times (~3 min) were obtained.

3.1.2. Effect of surfactant concentration

To perform the MEKC runs, surfactant concentration higher than the critical micelle concentration (CMC) must be used (CMC of SDS is 8 mM) [24].

The effects of different concentrations of SDS used (125–250 mM) were studied. Generally, increasing SDS concentration improves the separation efficiency but at the same time results in longer migration time (~5 min) and raises the current in the capillary (>140 μA). Therefore, 125 mM SDS concentration was chosen.

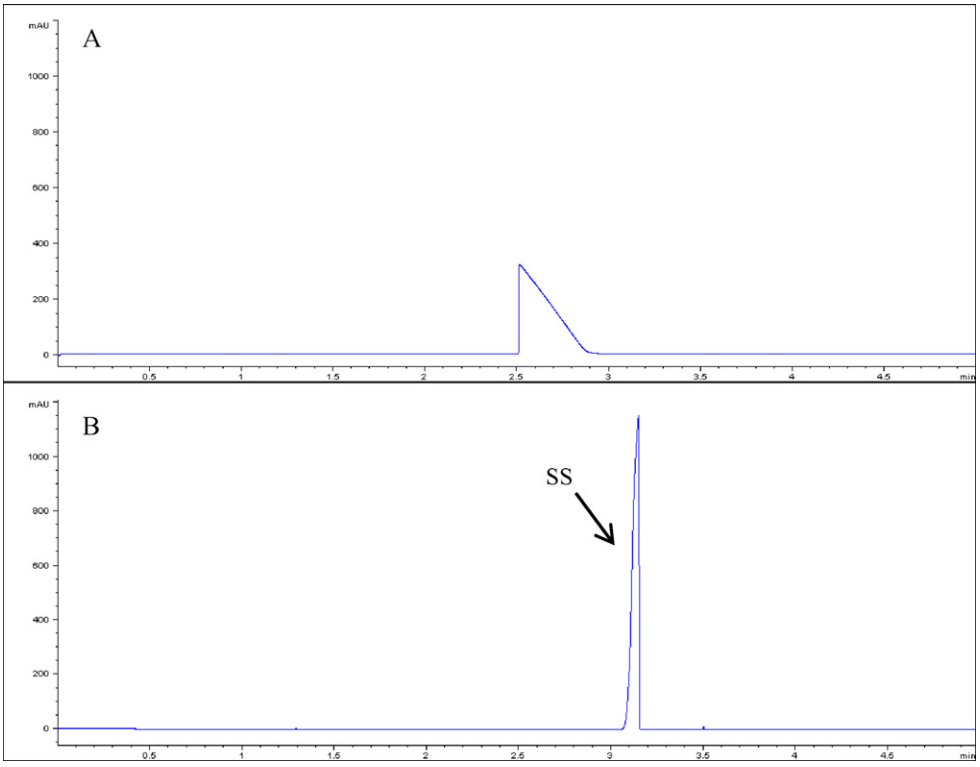


Fig. 2. Electropherogram showing the effect of sodium dodecyl sulfate (SDS) in peak enhancement: (A) BGE without SDS and (B) BGE with SDS (200 mM). BGE, 25 mM sodium dihydrogen phosphate—adjusted with concentrated phosphoric acid; temperature, 25 °C; and applied voltage, 24 kV, reversed polarity; injection time, 15 s. SS concentration, 500 μg mL^{-1}.

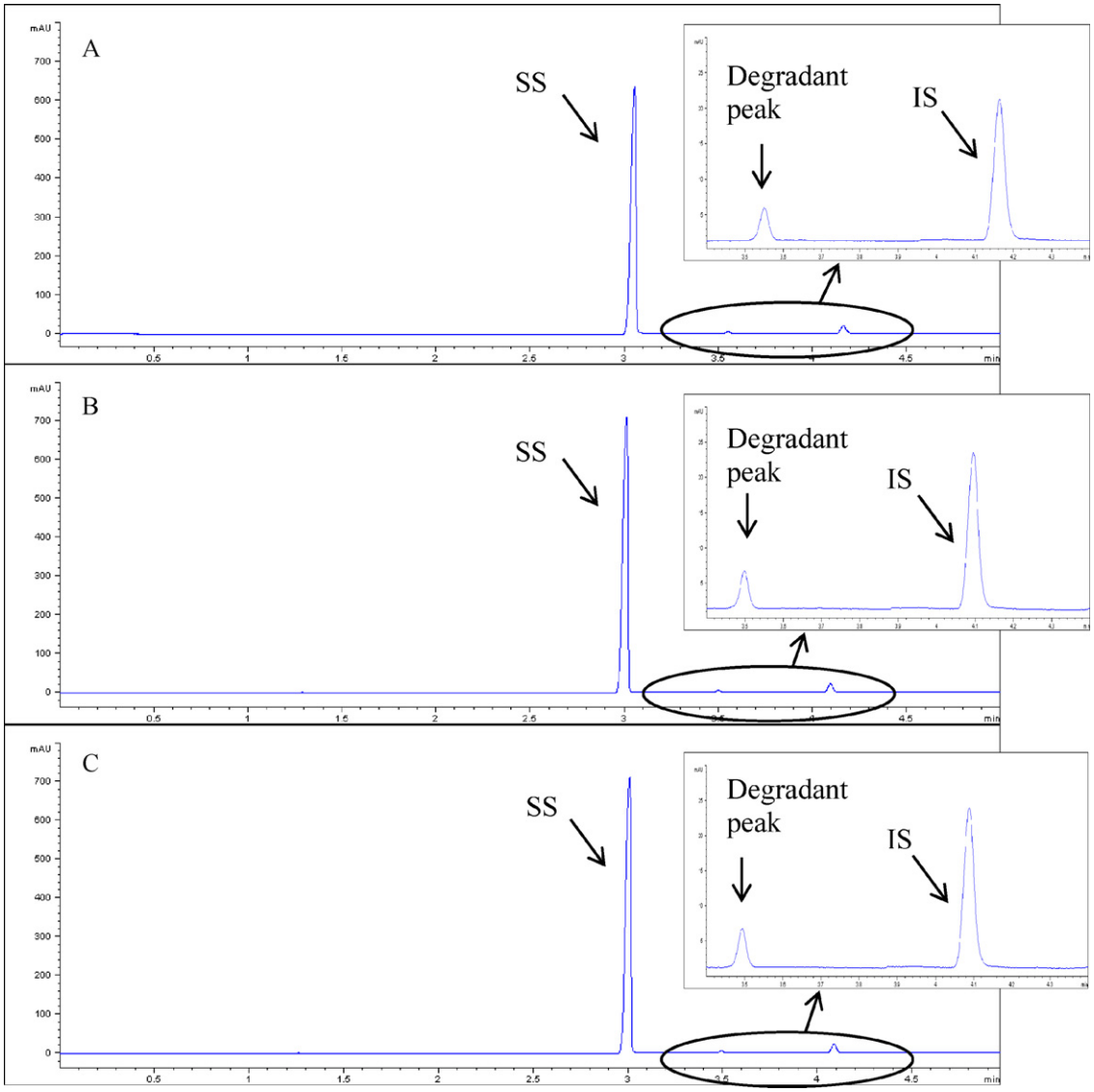


Fig. 3. Typical electropherograms obtained. Samples were heated in 0.1 M NaOH for (A) 2 h, (B) 4 h, and (C) 6 h. Please refer to text for MEKC conditions. SS concentration, 1000 μg mL^{-1}.

3.1.3. Effect of buffer concentration

The effect of concentration of sodium dihydrogen phosphate (25–100 mM) was investigated at constant pH 2.20. In general, buffer concentration affects the magnitude of the EOF. High buffer concentration reduces the EOF and vice versa. As a result, peak efficiency will decrease and the migration time (□4 min) will increase. Therefore, 25 mM of sodium dihydrogen phosphate was used for the next studies.

3.1.4. Effect of applied voltage

The effect of applied voltage was studied by varying the voltage from 18 to 28 kV. Increasing the voltage resulted in a shorter migration time. However, generation of joule heat may affect the resolution and peak efficiency when the voltage is increased [28]. Therefore, 26 kV was chosen for the next measurements as it gives reasonable migration time (□3 min) with good peak shape.

3.1.5. Effect of injection time

The effect of varying injection time was studied over the range (5–20 s) at 50 mbar. As the injection time was increased, peak area increased and as expected, peak broadening was noticed. Therefore, injection time of 10 s was used for the rest of the study as it gives good peak shape.

3.1.6. Effect of capillary temperature

The effect of varying capillary temperature (15–30 °C) on the peak efficiency was studied. Best peak were obtained when operated at 20 °C due to the good peak shape (lower Joule heating effect) and reasonable migration time. Fig. 4(A) shows typical electropherogram under the adopted electrophoretic conditions. It is clear that the selected electrophoretic conditions provide good quality peaks.

3.2. Validation of the analytical method

Validation was performed as outlined in the ICH guidelines [20]. In order to reduce the injection related-impression and to achieve better reproducibility and a greater control over the amount of sample introduced, the use of an (IS) in quantitative analysis is generally preferred [29]. Therefore phenobarbital as IS was selected to be used in this work.

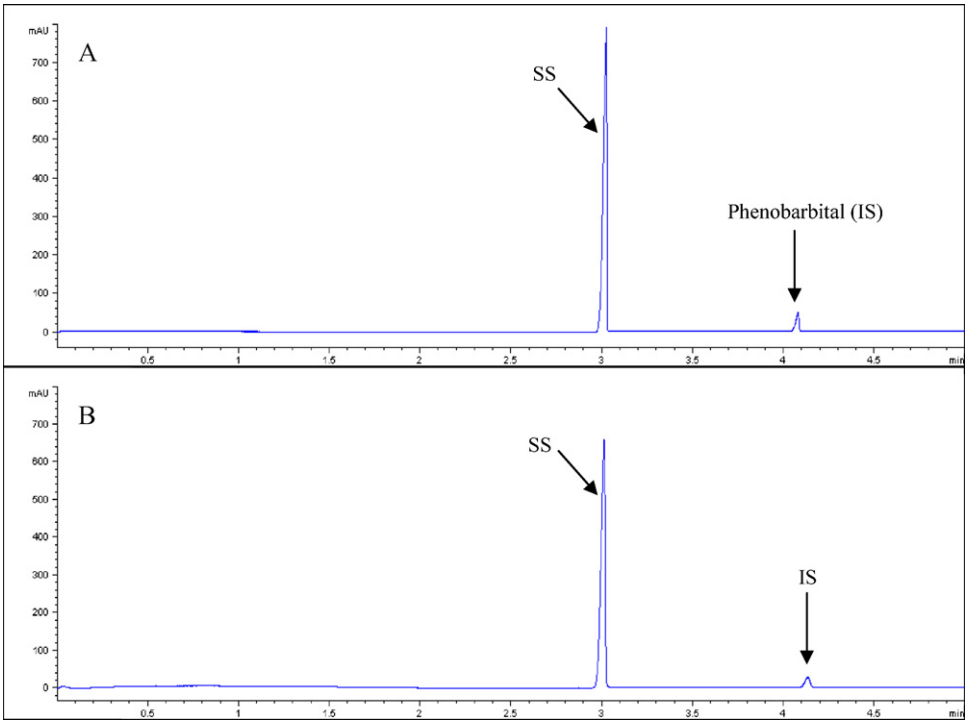


Fig. 4. Electropherograms obtained from the injection of SS standard (1000 μg mL^{-1}) (A); and Imigran tablet (1000 μg mL^{-1}) (B). Please refer to text for MEKC conditions.

3.2.1. Calibration curve, limits of detection and quantitation

Calibration curve was constructed by plotting the relative corrected peak area (y) versus the SS concentration (x) in μg mL^{-1}. Six standard solutions of SS were introduced in order to establish the linearity (100–2000 μg mL^{-1}). SS showed excellent linearity with the following regression equation:

$$y = 0.020x + 1.389, \quad r^2 = 0.999$$

The LOD of SS was 1.49 μg mL^{-1}. LOD was calculated as the sample amount introduced to yield a signal-to-noise ratio (S/N) of 3, and the LOQ was taken as the sample amount introduced to give a signal-to-noise ratio of 10. LOQ was found to be 4.50 μg mL^{-1}.

As expected, the sensitivity of the proposed CE method is inferior compared to the reported HPLC-UV methods [1,2] (LOD for SS was 10 and 3 ng mL^{-1}, respectively), or to the HPLC-fluorescence [3] (LOD was 1 ng mL^{-1}), or to the LC–MS [6,7] (LOQ was 0.7 and 0.2 ng mL^{-1}, respectively). However the analysis time of the proposed CE is slightly faster (<4 min compared to ~7.5 min in the CE report [13] or to the HPLC reports [1,2]). Although the sensitivity is inferior compared to the reported methods, nevertheless it posses adequate sensitivity for the analysis of the active ingredient in formulations.

3.2.2. Precision

Intra-day precision was assessed by introducing standard solutions of three concentrations (100, 500 and 2000 μg mL^{-1}). Each concentration was injected three times (n = 9). In all cases, the RSD for migration times, peak area, corrected peak area, ratio of corrected peak area and ratio of peak area were less than 0.68, 3.48, 3.28, 2.97 and 2.83%, respectively (Table 1). For inter-day precision, the three concentrations were injected for 3 successive days (n = 27). Also, the RSD for migration times, peak area, corrected peak area, ratio of corrected peak area and ratio of peak area were less than 2.01, 5.50, 4.46, 4.92 and 4.07%, respectively (Table 1).

3.2.3. Accuracy

The accuracy of the method was performed by conducting recovery test. It was carried out at three different concentrations (800, 1000 and 1200 μg mL^{-1}). Accurately weighed amounts of the placebo were dispersed in the standard solutions. The placebo concentration in the synthetic samples was fixed to be 6.0 mg mL^{-1}.

Table 1
Intra-day and inter-day precision and accuracy results for the determination of SS standard solutions.

Amount (μg mL^{-1})	RSD (%)					Amount (μg mL^{-1})	% Recovery ± SD (n = 9)
	Migration time	Peak area	Corrected peak area	Ratio of corrected peak area	Ratio of peak area		
Intra-day precision (n = 9)							
100	0.68	3.48	3.28	2.97	2.83	800	101.76 ± 3.04
500	0.50	2.72	2.52	1.00	2.23	1000	103.60 ± 1.71
2000	0.25	2.87	2.65	2.55	2.57	1200	104.72 ± 1.06
Inter-day precision (n = 27)							
100	0.73	4.06	4.34	4.92	3.71		
500	2.01	5.50	4.46	3.32	3.74		
2000	1.62	3.69	3.63	3.39	4.07		

n = no. of introductions to the CE system (three preparations for each concentration).

Table 2
Results for the determination of SS when subjected to different stressed conditions.

Analyte	Stress condition	% Recovery ± SD
SS	Water	
	2 h	97.58 ± 0.83
	4 h	97.51 ± 0.42
	6 h	90.38 ± 0.17
	10% H_2O_2	
	2 h	Complete degradation
	4 h	Complete degradation
	6 h	Complete degradation
	HCl 0.1 M	
	2 h	94.70 ± 0.73
	4 h	88.97 ± 1.50
	6 h	85.32 ± 0.57
	NaOH 0.1 M	
	2 h	91.15 ± 0.14
	4 h	86.03 ± 0.52
	6 h	83.74 ± 0.95
	UV exposure (254 nm)	
	2 h	96.67 ± 0.14

The values obtained suggested that good accuracy of the developed method for the determination of the SS in pharmaceutical formulation (Table 1). All samples were prepared and introduced in triplicates.

3.2.4. Specificity

No peaks were detected for the SS tablet placebo. Selectivity of the developed method was assessed by subjecting the SS standard to different degradation mediums as mentioned earlier. The degradation solutions were introduced to the CE analysis under the adopted conditions. Only the sample that was treated with NaOH showed a new peak. Moreover, the peak purity of SS was checked using the PDA detector equipped with the CE unit. Absorption spectra were obtained at the upslope, apex and down slope of the SS peaks. In all cases, the three overlaid UV spectra were the same, indicating peak purity and thus the selectivity of the developed method.

3.2.5. Analysis of pharmaceutical tablets

The developed method was applied for the determination of SS in commercially available SS tablet (Imigran 50 mg, Glaxo SmithKline). Results of the determination were found to be (104.58 ± 3.27)% (two preparations and each introduced twice to the CE system for the separation). Good agreement between the total value as claimed by the manufacturer and the developed CE method was obtained. Fig. 4(B) shows typical electropherogram of the pharmaceutical formulations.

3.2.6. Stressed degradation

SS was found to be stable under elevated temperature in water, 0.1 M NaOH, 0.1 M HCl and under UV light exposure. Under the oxidizing conditions, it was completely degraded (Table 2). It can be stated that no interferences either from excipients in the formulations or from the additional peak generated by the stress treatment interfered with the SS peak (Fig. 3), indicating the specificity of the developed method and its suitability to be used for routine work.

4. Conclusions

A MEKC method for the analysis of SS has been developed and validated in accordance with the ICH guidelines [20]. The degradation of SS under water, acidic, basic, oxidative and UV irradiation was studied. It was found that the drug was stable when exposed to UV irradiation at 254 nm and in water. However, the drug was rather unstable under the degradation stress of acidic and basic medium when refluxed at 80 °C for 6 h and was completely degraded under the oxidative conditions. The short overall run time has further proved that the analysis is rapid and cost effective. The stability indicating method was not interfered by tablet excipients. Higher separation efficiency and the minimization of use of solvents are other inherent features of the MEKC methods. Under the adopted conditions, baseline separation of SS and the internal standard were obtained in less than 4.5 min. Good analytical performance with regards to linearity, reproducibility, and accuracy was achieved.

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