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Stability-indicating methods for the determination of sumatriptan succinate

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Abstract

Four stability-indicating methods were developed for the determination of sumatriptan succinate in the presence of its degradation products. The first method depends on the quantitative densitometric evaluation of thin-layer chromatography of sumatriptan succinate in the presence of its degradation products without any interference. Cyclohexane–dichloromethane–diethylamine (50:40:10 v/v/v) was used as a mobile phase and the chromatogram was scanned at 228 nm. This method determines sumatriptan succinate in the concentration range 1–8 μg per spot with mean percentage recovery 100.52±1.23%. The second and third methods depend on the use of first-derivative (D_1) and second-derivative (D_2) spectrophotometry at 234 and 238 nm, respectively. These methods determine the drug in the concentration range 1.25–10 μg ml^{-1} with mean percentage recovery 99.91±1.01% and 99.96±1.13% for (D_1) and (D_2), respectively. The fourth method depends on the use of ratio derivative spectrophotometric technique. The amplitude in the first derivative of the ratio spectra at 235 nm was selected to determine the cited drug in the presence of its degradation products. Calibration graph is linear in the concentration range 1.25–10 μg ml^{-1} with mean percentage recovery 100.19±1.19%. The suggested methods were successfully applied for determining sumatriptan succinate in bulk powder, laboratory-prepared mixtures and pharmaceutical dosage forms (Imigran tablet) with good accuracy and precision. The results obtained by applying the proposed methods were statistically analyzed and compared with those obtained by the reported method.

Keywords: TLC-densitometry; Derivative spectrophotometry; Ratio spectra measurements; Sumatriptan succinate

1. Introduction

Sumatriptan succinate, 3-[2-(Dimethylamino) ethyl]-*N*-methyl-1H-indole-5-methanesulfonamide, is serotonin $5HT_1$-receptor agonist [1]. Its chemical structure and degradation products are shown in Fig. 1. Several methods have been reported for its determination in plasma and pharmaceutical formulations including colorimetry [2,3], HPTLC [3], polarography [4], capillary electrophoresis [5,6] and HPLC [7–14].

In the determination of the cited drug, the proposed methods are simple, fast, saving time

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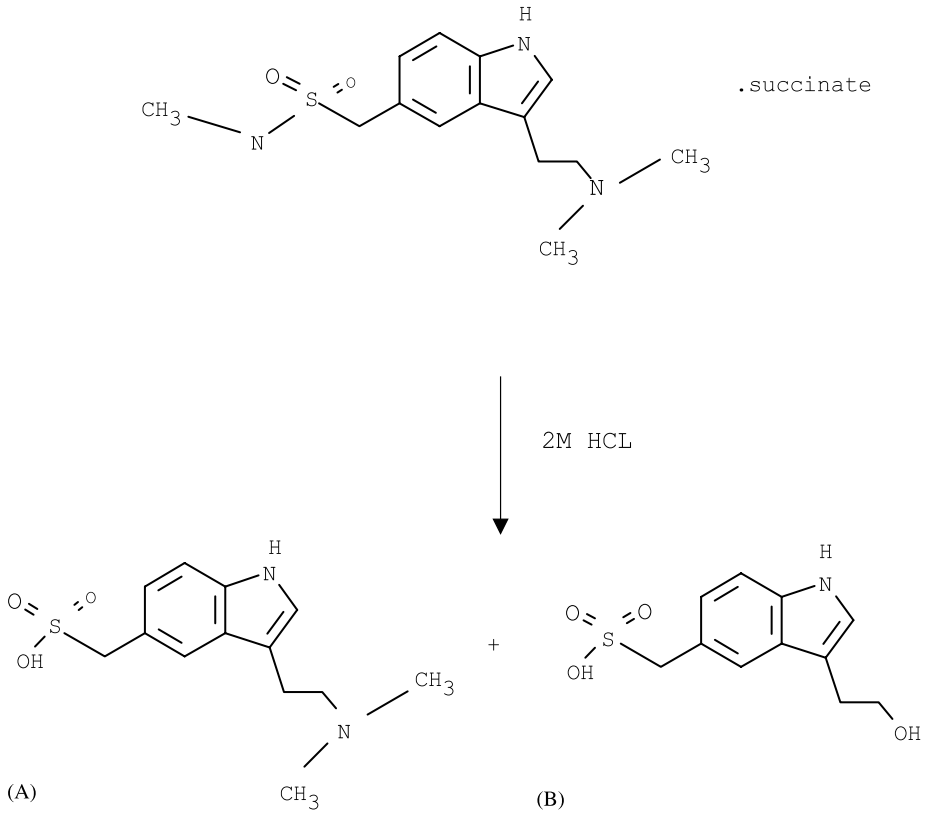


Fig. 1. Chemical structure of sumatriptan succinate and it's degradation products A and B.

and require minimum chemicals than the published colorimetric methods. Also, the proposed methods have the same sensitivity and more sensitive than the published methods except the HPLC method. Hence, the proposed methods are suitable for routine control analysis in a less equipped quality control laboratory.

The aim of this work was to introduce stability-indicating methods for the determination of sumatriptan succinate in the presence of its degradation products. Three methods have been introduced, derivative spectrometry, ratio derivative spectrometry and TLC densitometry. The obtained results were statistically compared with the reported method. The suggested methods were applied for determination of sumatriptan succinate in pure form, in pharmaceutical dosage forms and in the presence of its degradates.

2. Experimental

2.1. Apparatus

1) Densitometer—Dual wavelength SHIMADZU flying CS-9301.
2) UV lamp—short wavelength 254 nm.
3) Thin-layer chromatographic plates precoated with silica gel GF, 20×20 cm, 0.25 mm thickness, fluorescent at 254 nm (E. Merck Darmstadt Germany).
4) UV/VIS Spectrophotometer (SHIMADZU 1601/PC), with 1 cm quartz cuvettes, a fixed slit width (2 nm) connected to IBM-PC computer loaded with Shimadzu UVPC software with a Hewlett Packard printer and used for all the absorbance measurements and treatment of data.

2.2. Materials

Sumatriptan succinate, working standard, was kindly supplied by Glaxo Welcome Co., Cairo, Egypt. The purity of the sample was found to be 99.56 ± 1.43% according to the reported method [12].

Imigran tablets (Glaxo Welcome Co.); batch No.81641. Each tablet was labeled to contain:

140 mg (100 mg base) of sumatriptan succinate;
140 mg lactose;
15.5 mg microcrystalline cellulose;
3.0 mg croscarmellose sodium Type A;
1.5 mg magnesium stearate.

2.3. Reagents

All chemicals were of analytical grade and all solvents were of spectroscopic grade.

1) Mobile phase: cyclohexane–dichloromethane –diethylamine (50:40:10 v/v/v).
2) Methanol.
3) Sodium hydroxide, 2 M, aqueous solution.
4) Hydrochloric acid, 2 M, aqueous solution.

2.4. Preparation of degradation products

50 mg of sumatriptan succinate was dissolved in 10 ml methanol in a conical flask. 50 ml of 2 M hydrochloric acid was added and placed on a water bath at 80 °C for 24 h. The solution was neutralized with 2 M sodium hydroxide and evaporated on a water bath to a few milliliters. 10 ml of methanol was added and filtered if necessary. The methanol solution was applied in a band form to TLC plates and 20 μl of standard solution in methanol (1 mg ml^{-1}) was also spotted as a reference. The plates were developed in a chromatographic chamber previously saturated with the mobile phase cyclohexane–dichloromethane–diethylamine (50:40:10 v/v/v) for 15 min by ascending chromatography through a distance of about16 cm and then air-dried. The two bands corresponding to degradation products were visualized under UV light at 254 nm, each band was scrapped and extracted three times each with 10 ml portion of methanol. The extracts were filtered and evaporated just to dryness on a boiling water bath. The residue left after evaporation was weighed, dissolved in methanol to get a concentration of 1 mg ml^{-1} and used for the preparation of laboratory-prepared mixtures.

2.5. Stock standard solutions

The solution was stable for at least 5 days if it had been stored in refrigerator.

1) Sumatriptan succinate 1 mg ml^{-1} in methanol for densitometric method.
2) Sumatriptan succinate 50 μg ml^{-1} in methanol for first-derivative, second-derivative and first-derivative of ratio spectra methods.
3) Sumatriptan succinate degradation products 1 mg ml^{-1} for densitometric method.
4) Sumatriptan succinate degradation products 50 μg ml^{-1} in methanol for first-derivative, second-derivative and first-derivative of ratio spectra methods.

2.6. Laboratory-prepared mixtures

2.6.1. Densitometric method

Aliquot equivalent to 0.5–4.0 mg of sumatriptan succinate from its stock standard solution (1 mg ml^{-1}) were transferred into series of 5 ml volumetric flasks. 10–90% of degradation products (1 mg ml^{-1}) solution were added to the same flasks.

2.6.2. Derivative and ratio derivative spectrophotometric methods

Aliquot equivalents to 12.5–100.0 μg of sumatriptan succinate from its stock standard solution (50 μg ml^{-1}) were transferred into series of 10 ml volumetric flasks. 10–90% of degradation products (50 μg ml^{-1}) solution were added to the same flasks.

2.7. Procedures

2.7.1. Construction of calibration curves for densitometric method

Aliquots of stock standard solution (1 mg ml^{-1}) equivalent to 0.5–4.0 mg of sumatriptan succinate were transferred into series of 5 ml volumetric flasks and diluted to volume with methanol. 10 μl of each solution was applied to TLC plate and the plate was developed to 16 cm. Using the developing mobile phase, cyclohexane–dichloromethane–diethylamine (50:40:10 v/v/v). The plate was removed, air dried and the spots were visualized under UV lamp at 254 nm. The chromatogram was scanned with spectrodensitometer at 228 nm. The calibration curve representing the relationship between the recorded area under the peak and the corresponding concentration was plotted and the regression equation was calculated.

2.7.2. Construction of calibration curves for first and second derivative spectrophotometric methods

Aliquots of stock standard solution (50 μg ml^{-1}) equivalent to 12.5–100.0 μg of sumatriptan succinate were transferred into series of 10 ml volumetric flasks and completed to volume with methanol. The first-derivative (D_1) and second-derivative (D_2) curves were recorded for each solution using methanol as a blank with $A\lambda = 2$ and 8 and scaling factor 1 and 10, respectively. The (D_1) and (D_2) values were measured at 234 and 238 nm, respectively. The calibration curves were constructed and the corresponding regression equations were calculated.

2.7.3. Construction of calibration curves for first-derivative of ratio spectra method

Aliquot equivalent to 12.5–100.0 μg from its stock standard solution (50 μg ml^{-1}) were transferred into series of 10-ml volumetric flasks and completed to volume with methanol. The spectrum for each solution was divided by the spectrum of standard solution of its degradation products (9 μg ml^{-1}). All spectra were stored in the IBM\PC. The first-derivative of each ratio spectra obtained was recorded with $A\lambda = 4$ and the (DD_1) value was measured at 235 nm. The calibration curve was constructed and the regression equation was calculated.

2.7.4. Assay of pharmaceutical formulations (tablets)

Ten tablets of sumatriptan succinate were accurately weighed and finely powdered. An amount of the powder equivalent to 100.0 mg of the drug was weighed, dissolved 3×25-ml methanol by shaking in ultrasonic bath for about 15 min. The solution was filtered each time and transferred quantitatively into 100-ml volumetric flask. The volume was then completed to the mark with methanol (1 mg ml^{-1}). The assay was completed as described above. The concentration was obtained from the corresponding regression equations.

3. Results and discussion

3.1. Densitometric method

In this work, TLC densitometric method was used for the determination of sumatriptan succinate in presence of its degradation products depending on the difference in R_f values.

Complete separation was obtained using cyclohexane: dichloromethane: diethyl amine (50:40:10 v/v/v) as a mobile phase. The R_f values of the drug and its degradation products were 0.17, 0 and 0.32, respectively.

A linear calibration curve was obtained in the concentration range 1.00–8.00 μg per spot with mean percentage recovery 100.52 ± 1.23. The parameters of regression equation are shown in Table 1.

The proposed TLC method is very simple, rapid and use minimal volume of solvents compared with the other separation techniques. Furthermore, an extremely large numbers of samples can be analyzed at the same time without compromising accuracy, the proposed method is thus suitable for quality control laboratories, where economy and time is essential.

Table 1
Characteristic parameters for the regression equations of TLC densitometry, first derivative (D_1), second derivative (D_2) and first derivative of the ratio spectra (DD_1) methods for the determination of sumatriptan succinate in the presence of its degradation products

Parameters	TLC method	(D_1) method	(D_2) method	(DD_1) method
Linearity[a] (μg ml^{-1})	1.00–8.00	1.25–10.00	1.25–10.00	1.25–10.00
Regression equation (y)[b]				
Slope (b)	6.355	0.0152	0.0024	0.8298
R.S.D. of the slope	0.029	2.88×10^{-4}	2.51×10^{-4}	3.46×10^{-4}
Intercept (a)	1.4475	−0.0001	0.0001	0.2461
R.S.D. of the intercept	2.94×10^{-4}	2.39×10^{-5}	1.64×10^{-5}	3.74×10^{-4}
Correlation coefficient	0.9999	0.9999	0.9999	0.9995
LOD	0.50	0.70	0.82	0.88
LOQ	0.80	1.00	1.20	1.24

[a] Concentration range, LOD, LOQ in μg ml^{-1} for derivative spectrophotometric methods and in μg per spot for TLC densitometry.
[b] $Y = a + bc$, where c is the concentration of drug in μg ml^{-1} and Y is the amplitude at the specified wavelength in derivative spectrophotometry and area under the peak in TLC densitometric method.

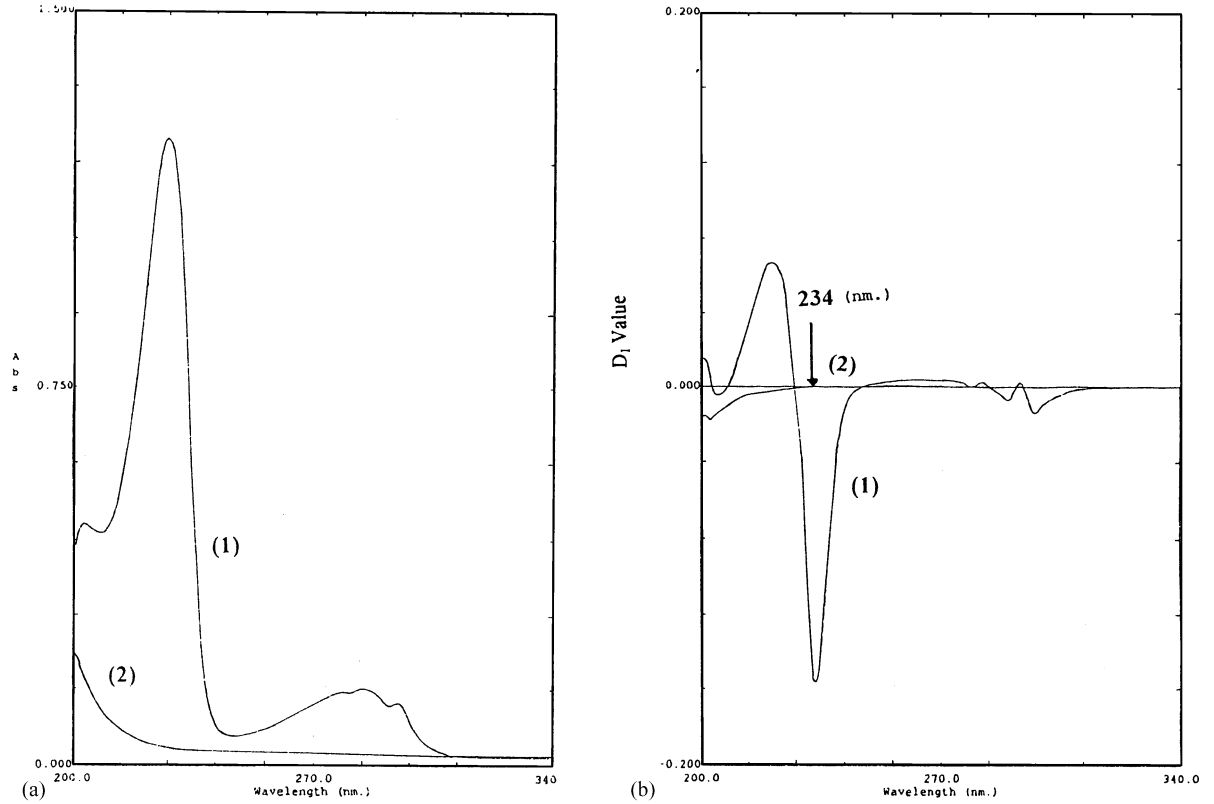


Fig. 2. (a) UV scanning of zero-order of intact sumatriptan succinate and its degradation products. (b) UV scanning of first-derivative of intact Sumatriptan succinate. (1) Intact sumatriptan succinate, 10 μg ml^{-1} in methanol. (2) Degradation products, 10 μg ml^{-1} in methanol. (c) UV scanning of second-derivative of intact sumatriptan succinate and its degradation products. (1) Intact sumatriptan succinate, 10 μg ml^{-1} in methanol. (2) Degradation products, 10 μg ml^{-1} in methanol.

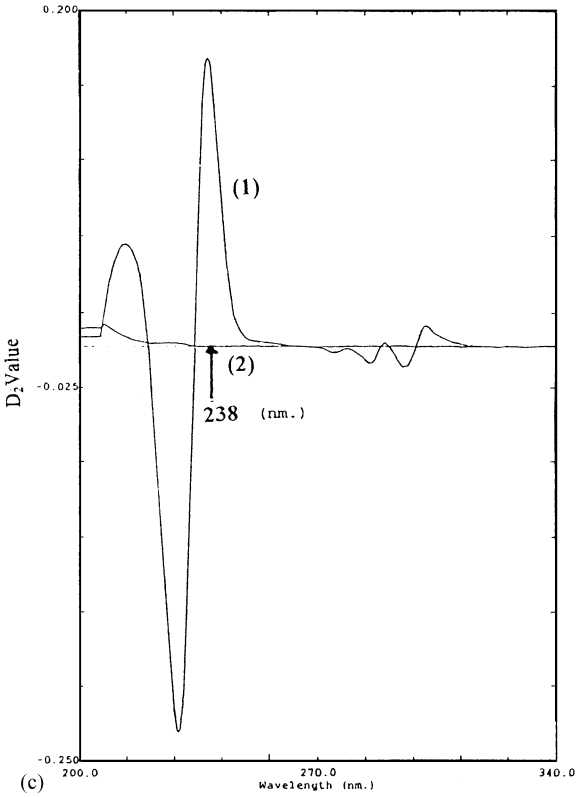


Fig. 2 (*Continued*)

3.2. Derivative spectrophotometric methods

In this work, three different derivative spectrophotometric techniques were applied for quantitative determination of sumatriptan succinate; these techniques are first-derivative (D_1), second-derivative (D_2) and first-derivative of ratio spectra (DD_1).

The zero-order spectra (D_0) of the drug and its degradation products showed a marked overlapping; (Fig. 2a), which interfere with the analysis of the drug. The (D_1) and (D_2) were applied which intern allowed better resolution, (Fig. 2b and c).

By the application of the first-derivative of the ratio spectra (DD_1) sumatriptan succinate can be quantitatively determined at 235 nm without any interference from its degradation products, (Fig. 3).

Careful choice of the divisor and the working wavelength were of great importance so different concentrations of degradation products were tried as a divisor (1, 5 and 9 μg ml^{-1}), the best one was 9 μg ml^{-1} as it produces minimum noise and gives better results in accordance with selectivity.

Linear calibration curves were obtained for the three methods in the concentration range 1.25–10.00 μg ml^{-1} with mean percentage recoveries 99.91 ± 1.01, 99.96 ± 1.13 and 100.19 ± 1.19 for (D_1), (D_1) and (DD_1), respectively.

The characteristic parameters of regression equations and correlation coefficients are given in Table 1.

The accuracy of the proposed methods were checked by analyzing nine laboratory-prepared mixtures of sumatriptan succinate in presence of its degradation products in different ratios, Table

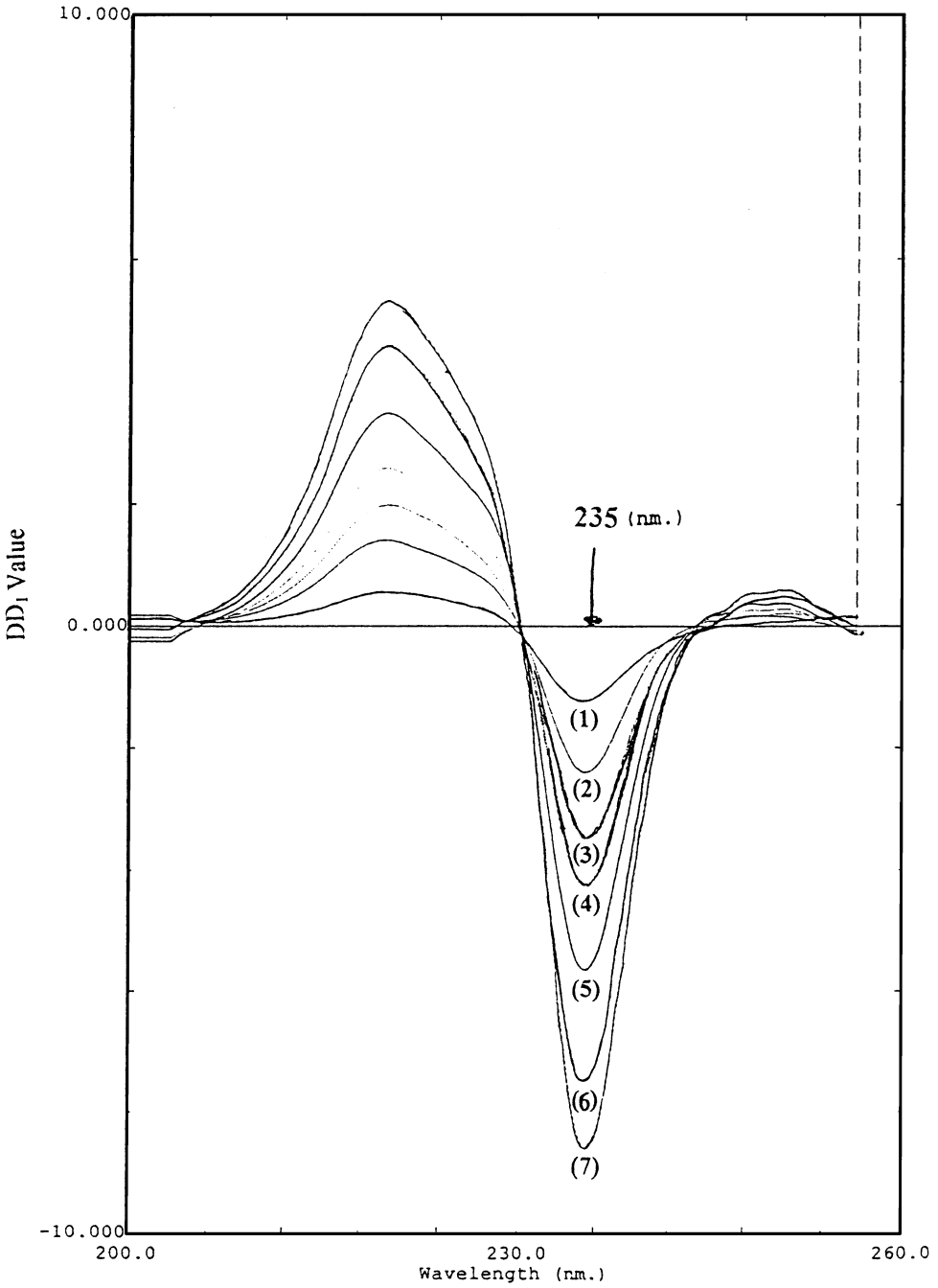


Fig. 3. UV scanning of first-derivative of the ratio of spectra of Sumatriptan succinate in mentanol (1) 1.25 μg ml^{-1}, (2) 2.50 μg ml^{-1}, (3) 3.75 μg ml^{-1}, (4) 5.00 μg ml^{-1}, (5) 6.25 μg ml^{-1}, (6) 8.75 μg ml^{-1}, (7) 10.00 μg ml^{-1} using 9.00 μg ml^{-1} of it's degradation products as a divisor.

Table 2
Comparison of the proposed methods and reported method for the determination of sumatriptan succinate in the presence of its degradation products

Sample number	% of degradation products[b]	TLC method found (%)[a]	D_1 method found (%)[a]	D_2 method found (%)[a]	DD_1 method found (%)[a]	Reported method[c] found (%)
1	10	101.06	100.00	100.00	97.44	99.10
2	20	100.67	101.72	100.00	98.96	101.21
3	30	99.11	97.67	100.00	97.71	99.50
4	40	99.45	100.00	100.00	97.19	99.67
5	50	98.92	100.00	100.00	97.66	100.25
6	60	101.00	101.14	100.00	98.27	98.87
7	70	99.76	100.49	97.29	100.95	101.00
8	80	98.97	100.44	100.00	101.11	100.81
9	90	100.76	101.60	100.00	101.35	99.11
Mean ± C.V. (%)		99.97 ± 0.90	100.34 ± 1.21	99.70 ± 0.90	98.96 ± 1.71	99.95 ± 0.89

[a] Found % of pure sample.
[b] Calculated with respect to the total weight (drug-degradation mixture).
[c] The reported method is the HPLC method using Hypersil C18 column, phosphate buffer of pH(6)/acetonitrile (4:1) as a mobile phase and detection at 227 nm.

Table 3
Determination of pharmaceutical dosage forms of the cited drug by the proposed methods and the reported method [12]

Pharmaceutical preparation	TLC method		D_1 method		D_2 method		DD_1 method		Reported method [12]
	Found[a] ± R.S.D. (%)	Recovery ± R.S.D. (%)	Found[a] ± R.S.D. (%)	Recovery ± R.S.D. (%)	Found[a] ± R.S.D. (%)	Recovery ± R.S.D. (%)	Found[a] ± R.S.D. (%)	Recovery ± R.S.D. (%)	Found[a] ± R.S.D. (%)
Imigran tablets 100 mg per tablet B.N. 81641	99.98 ± 0.63	100.39 ± 0.23	99.78 ± 0.38	100.77 ± 0.69	99.37 ± 1.09	100.38 ± 0.66	98.96 ± 1.50	100.84 ± 1.00	99.95 ± 1.26
F (19.00)[b]	3.98		11.36		1.34		1.42		
T (2.776)[b]	0.03		0.18		0.49		0.71		

[a] Average of six analytes.
[b] The values between parenthesis are corresponding to the theoretical values of t and F at the 95% confidence level.

Table 4
Statistical comparison of results for the determination of Sumatriptan succinate by the proposed and the reported methods

Values	TLC method	D_1 method	D_2 method	DD_1 method	Reported method [12][b]
Mean ± C.V.	100.52 ± 1.23	99.91 ± 1.01	99.96 ± 1.13	100.19 ± 1.19	99.56 ± 1.43
N	6.00	6.00	6.00	6.00	6.00
Variance	1.51	1.02	1.28	1.42	2.04
t (2.23)[a]	1.25	0.49	0.54	0.67	
F (5.05)[a]	1.35	2.00	1.59	1.44	

[a] The values between parenthesis are corresponding to the theoretical values of t and F at the 95% confidence level.
[b] HPLC method using hypersil C_{18} column, phosphate buffer pH6, acetonitrile (4:1) as a mobile phase and UV detection at 227 nm.

2. Satisfactory recoveries with small relative standard deviations (S.D.) were obtained, which indicated the high repeatability and accuracy of the proposed methods.

The proposed methods were also successfully applied for the analysis of the drug in pharmaceutical dosage forms and the results are shown in Table 3.

The validity of the proposed methods was assessed by applying the standard addition technique. The results obtained were reproducible with low S.D. as shown in Table 3, and the mean recovery was compared with that obtained by the reported method, in order to demonstrate the validity and applicability of the proposed methods. There was no evidence of interference from the excipients.

Table 4 shows the statistical comparison of analytical results for pure samples by the proposed methods and reported one [12]. Calculated t and F values are less than the theoretical ones, indicating with 95% confidence limit that there is no significant difference between the proposed and the reported methods with respect to accuracy and precision.

3.3. Identification of degradation products

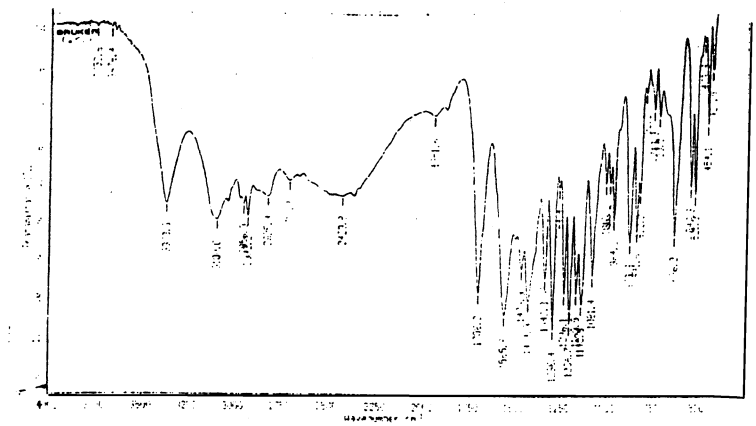
The degradation product of sumatriptan succinate was prepared in the laboratory by hydrolysis with 2 M hydrochloric acid and separated by TLC using cyclohexane–dichloromethane–diethyleamine (50:40:10 v/v/v) as a developing system. Two spots were appeared for the degradation products one spot at $R_f = 0$ and the other at $R_f = 0.32$. The suggested degradation products of sumatriptan succinate may occur partially at the sulfonamide moiety to give the degradation product (A) or may occur completely at both the sulfonamide and the 3° amine moieties to give the second degradation product (B) as shown in Fig. 1. The degradation products (A) and (B) were elucidated by IR spectrum as shown in Fig. 4.

The IR spectrum of (A) indicates the disappearance of sharp N–H peak at 3373 $cm^{-1}$of the authentic sample and appearance of sulphonate moiety at 2974–2775 cm^{-1} in addition to the N–H of indole at 3395 cm^{-1}.

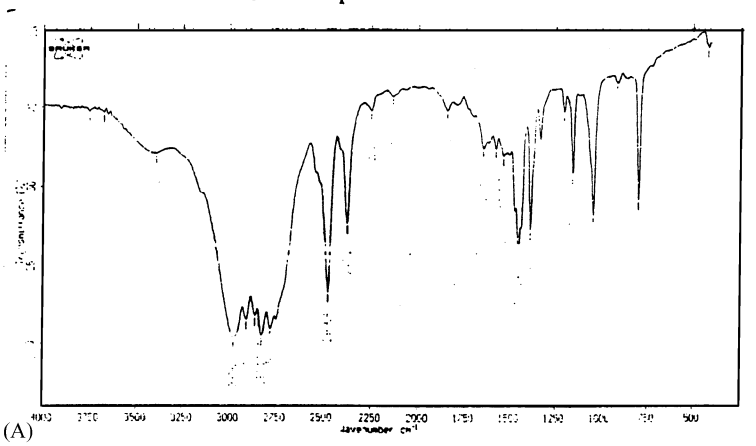
The IR spectrum of (B) indicates the presence of broad peak at 3422 cm^{-1} due to OH association in addition to a peak corresponding to sulphonate moiety at 2965–2775 cm^{-1}.

4. Conclusion

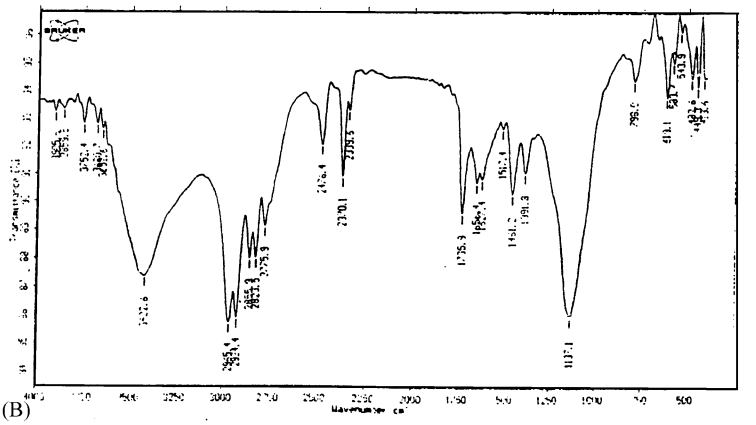
The suggested methods can be used as stability-indicating method for the determination of sumatriptan succinate in presence of its degradation products and in commercial formulations without interference from tablets excipients. In addition, these methods have a potential for application in quality control laboratories, as it is simple, rapid and not need to complicated instruments and show good accuracy and precision. The proposed methods have the same sensitivity. The derivative spectrophotometric methods have the advantages of the low cost, speed and simplicity than TLC densitometric method.



sumatriptan succinate



(A)



(B)

Fig. 4. (a)(b) IR spectrum of degradation products (A and B) (c) IR spectrum of sumatriptan succinate.

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