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Original Article

MICELLAR ENHANCED SYNCHRONOUS FLUORESCENCE FOR THE ASSAY OF SUMATRIPTAN SUCCINATE IN PHARMACEUTICAL TABLETS

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ABSTRACT

Objective: To develop a sensitive, fast and selective method for the determination of sumatriptan succinate (SUM) in pharmaceutical samples.

Methods: The method is based on measuring the synchronous fluorescence of SUM using Δλ of (12 0 nm) and at a wavelength of excitation and emission of 230 and 325 nm respectively, using Agilent Technology, Cary eclipse, G9800AA model Luminescence spectrometer. Effect of variables on fluorescence emission intensities was studied such as solvent, surfactant, and pH. The proposed method was validated in term of linearity, limit of detection as per the international conference on harmonization guidelines ICH Q_2 (R1).

Results: The linearity of the method was obtained with a wide range of (50-150) ng/ml with a high value of correlation coefficient value of (0.992). Limits of detection (LOD) and limits of quantitation (LOQ) were found to be 16.3 and 49.5 ng/ml respectively, the mean recovery was found to be 99.1% with low relative standard deviation (% RSD). The method was also compared statistically with the reference method using t-test and f-test, the results show no difference either in pure or pharmaceutical tablets.

Conclusion: The obtained results revealed that the developed method can be applied successfully for the determination of SUM in drug formulations samples with good accuracy and precision.

Keywords: Sumatriptan, Spectrofluorimetry, Pharmaceutical preparations

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INTRODUCTION

Triptans are used for the treatment of prophyllaxis and acute migraine headaches in human, the most commonly used drug among triptans is sumatriptan succinate (fig. 1) it is chemically 3-[2-(diaminoethyl)]-N-methyl-indole-5-methane sulfonamide succinate. sumatriptan is a specific and selective 5-hydroxyl tryptan receptor (5HT1D) agonist with no effect on other 5HT receptor (5HT2-5HT7) subtypes.

It is official in European pharmacopeia [1] and United States pharmacopeia [2].

Several methods were suggested for the determination of sumatriptan in different types of samples, including, UV [3], spectrophotometric [4-6], other methods were based on high-performance liquid chromatography with various detecting systems such as UV detection [7], fluorescence detection [8] and MS detection [9, 10]. Other methods were based on and voltammetry [11]. Few methods were based on the fabrication of nanomaterial-based sensing methods [12-14]. According to the previous methods, it can be seen that most of them are based on using expensive and sophisticated techniques, this encourages us to develop a simple method for the assay of sumatriptan in the pharmaceutical samples. Spectrophotometric methods are widely used in the pharmaceutical analysis, but they have poor selectivity and sensitivity compared to spectrofluorimetry [15, 16]. The developed method is based on the enhancement of the intrinsic Fluorescence of SUM, then measuring Synchronous Fluorescence intensities in different media. All the factors affecting the fluorescence intensities were studied, including the type of solvent, pH, temperature and micellar additives. The developed methods were validated and applied to real pharmaceutical samples and were compared with official methods. Synchronous fluorescence technique has many priorities compared to conventional fluorescence spectroscopy, including simple spectra, higher selectivity, sensitivity and lower interferences which are due to sharper and narrower fluorescence peaks [17-19]. It is well known that the presence of surfactants may increase the rigidity of the molecules being surrounded by the surfactant which restricts the movement of the fluorophore and so decrease the energy transfer to the surrounding environment, As a result, increases the quantum yield and enhance the fluorescence intensity of the guest molecules [21, 23]. The anionic surfactant sodium lauryl sulfate (SLS) has recently found many applications in emission fluorescence enhancement and applications for the determination of some pharmaceutical compounds [24].

The developed method is considered as a low cost, a time-saving and sensitive method that has the advantages of not using derivatization reactions using toxic chemicals. Moreover, another method of the conventional spectrofluorimetric technique was applied using the synchronous scanning fluorescence at (Δλ = 120 nm), which allowed a simpler spectrum with less overlapping [24].

The developed method was validated and applied successfully for the quantitative determination of (SUM) in pharmaceutical samples.

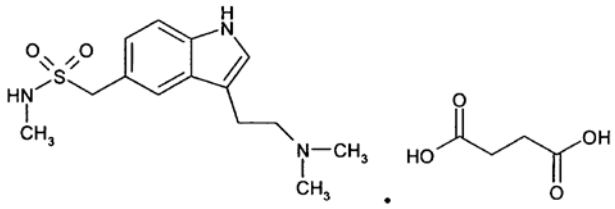

Fig. 1: Chemical structure of sumatriptan succinate

MATERIALS AND METHODS

Apparatus

Fluorescence intensities were measured using Agilent Technology, Cary eclipse, G9800AA model Luminescence spectrometer (Australia) equipped with a xenon arc lamp, The slit width for excitation and emission measurements were set at 5.0 nm and measured simultaneously with a constant Δλ scan (λ_{emi}-λ_{exi}) of 120 nm. A 1.0 cm quartz cell was used at 25.0 °C. A pH meter (HANNA model: HI 2211) was used for all pH measurements.

Materials and reagents

Reagents used were of analytical grade and deionized water was used throughout. Pure grade sumatriptan succinate were kindly supplied from Egyptian company. The pharmaceutical preparations were purchased from local drug stores oratab®100 mg tablet Tabouk company-Saudi Arabia. Sodium lauryl sulfate (SLS) 96 %, Tween 80, *β*-cyclodextrin, glacial Acetic acid were from BDH laboratory supplies, sodium acetate, sulphuric acid. Analytical grade solvents: acetonitrile 99.5%, methanol 99.9% dioxan 99% were obtained from Sharlau-Spain.

Standard solution

Stock solution of SUM was prepared by dissolving 0.01 g in 100 ml deionized water, then further dilutions were prepared using the given diluting solvents as appropriate and kept in the refrigerator.

General procedures

Calibration graphs

Aliquots of SUM standard solution were transferred into a series of 10-ml calibrated volumetric flasks, then 1 ml of 0.2 M acetic acid/acetate buffer of pH (5.5) was added, followed by 0.5 ml 2% SLS, mixed and then diluted to the mark using methanol as a diluting solvent to give a final concentration of (50-150 ng/ml). Then stored in the refrigerator at 10 °C for 15 min, after that the Fluorescence intensity was measured at appropriate excitation and emission wavelengths corresponding to the selected diluting solvent. The calibration curves were constructed by plotting the fluorescence intensity versus SUM concentration (ng/ml) and the regression equations were obtained.

Analysis of tablet samples

The contents of ten tablets were crushed and powdered, then a mass equivalent to 10.0 mg was weighed and transferred into a 100 ml volumetric flask, about 75 ml of methanol was added, the mixture was sonicated for 10 min, then the volume is completed to 100 ml with methanol, mixed and filtered through a 0.45 µm membrane filter. Serial dilutions covering the working concentration range of (50-150 ng/ml) were transferred into a series of 10.0 ml volumetric flasks. Then the procedure mentioned in the preparation of calibration graph was followed.

RESULTS AND DISCUSSION

Spectrofluorimetic methods of analysis are considered as sensitive and simple for the determination of many pharmaceutical active species in different samples [25, 26]. To our knowledge there is no analytical method based on native fluorescence of SUM, in this study, it was found that SUM exhibits an emission fluorescence spectrum at about 350 nm after excitation at 225 nm in aqueous medium (fig. 2) So there is a need to investigate the effect of different media on such behavior, because of its relatively low relative fluorescence intensity (RFI). It is important to develop a simple and sensitive spectrofluorimetric method for the determination of SUM in a different type of samples. In this study, various experimental factors that influence the RFI of SUM were studied in order to decrease the detection limit. So different factors were studied as follow:

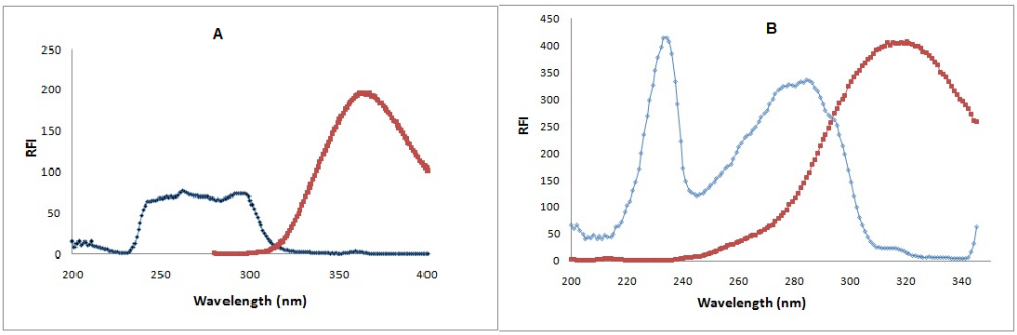

Fig. 2: Fluorescence spectra of SUM (100 ng/ml) in 10.0 ml of water (A) and methanol (B)

Effect of diluting solvent

In order to study the effect of different media on the enhancement of fluorescence intensity, different organic solvents were used as diluting solvents including acetonitrile, methanol, ethanol, and dioxan. It was found that the fluorescence intensity is enhanced with the order of methanol, acetonitrile, dioxan and then ethanol as can be seen in (fig. 3). This behavior is probably due to the dynamic stabilization of the studied drug. The emission wavelengths of SUM in dioxan were 275 and 350 for acetonitrile and 294 nm for methanol. The excitation wavelength were 298, 262 nm and 253 nm of the three solvents respectively.

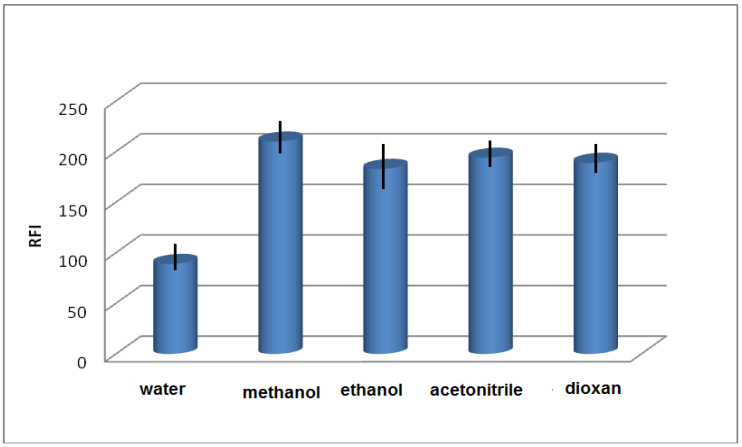

Fig. 3: Effect of diluting solvent on RFI of 10.0 ml solution of SUM (100 ng/ml), error bars represent the standard deviation of three experiments

Effect of organized media

For the better enhancement of the analytical characteristics of the fluorescence spectra of SUM, a study of the effect of different types of surfactants (cationic, anionic and nonionic) and beta-cyclodextrin was performed using the different effect of equal volume each surfactant used were summarized in (fig. 4), it can be shown that SLS gave the best enhancement of the RFI which is due to the dynamic properties of limited movement of the micellar medium of SUM [25].

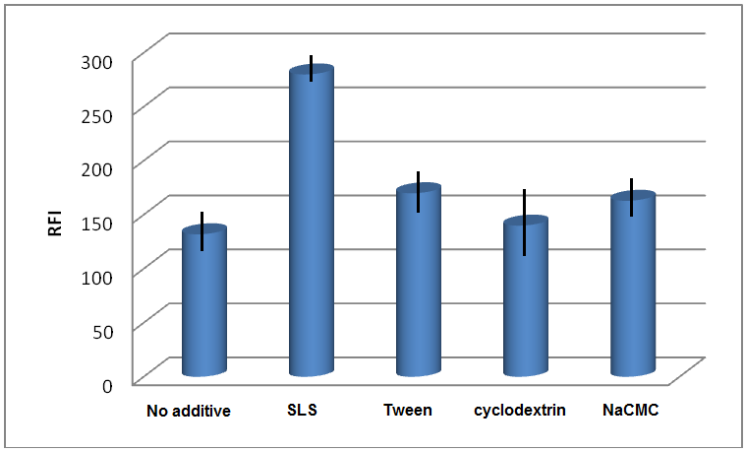

Fig. 4: Effect of the addition of organized media on RFI of SUM (100 ng/ml), 10.0 ml sample, after the addition of 1 ml of 0.5% of each medium of the RFI of SUM. Error bars represent the standard deviation of three experiments

Effect of pH

The effect of pH values on the fluorescence intensity was studied by using different values of pH prepared by different buffer solutions with methanol as a diluting solvent and SLS surfactant, it was found that the maximum value of fluorescence intensity was obtained at pH around 5 using acetate buffer as shown in (fig. 5), which is probably due to the formation of a non-ionizable form of the studied drug at this pH value.

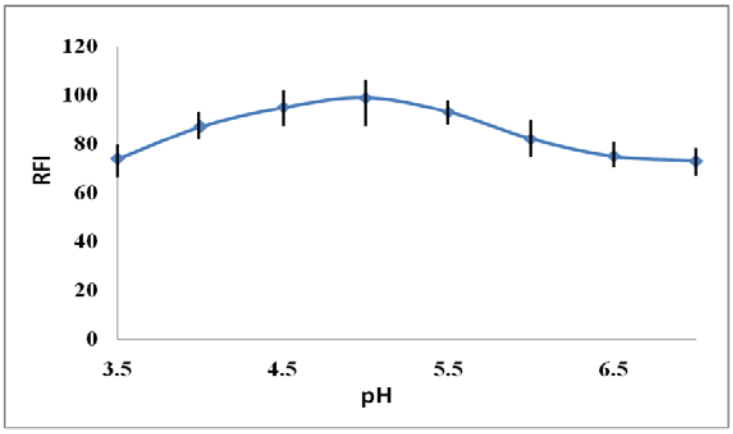

Fig. 5: Effect of pH on RFI of SUM (100 ng/ml) using acetate buffer, error bars represent the standard deviation of three experiments

In order to minimize the broadening of the emission fluorescence peaks and thus possible overlapping and minimize scattering. An alternative method for the conventional fluorescence spectrum is the use of synchronous scanning fluorescence. In this technique, the excitation and emission monochromator were scanned simultaneously and the emission intensity is recorded as a function of the excitation wavelengths. The difference between $\lambda_{em.}$ and $\lambda_{ex.}$ ($\Delta\lambda$) is a very important factor in the synchronous spectrum for determining the position of the bands and their intensities. In the present work the optimization of ($\Delta\lambda$) was performed by selecting different values of $\Delta\lambda$ then interpretation of the fluorescence spectrum, as a result $\Delta\lambda$=120 nm was selected because it gave sharper peak with maximum intensity, least peak overlap and increase in (RFI) as a function of concentration of SUM as shown in (fig. 6) below.

Validation of the proposed method

The developed method was validated using the following parameters: Linearity, sensitivity, LOD, LOQ, specificity, accuracy and precision.

Linearity and range

A linear relationship was established for SUM by plotting relative fluorescence intensities against different drug concentrations, the calibration curve was linear over the range 50-150 ng/ml with a high value of correlation coefficient (r) table 1.

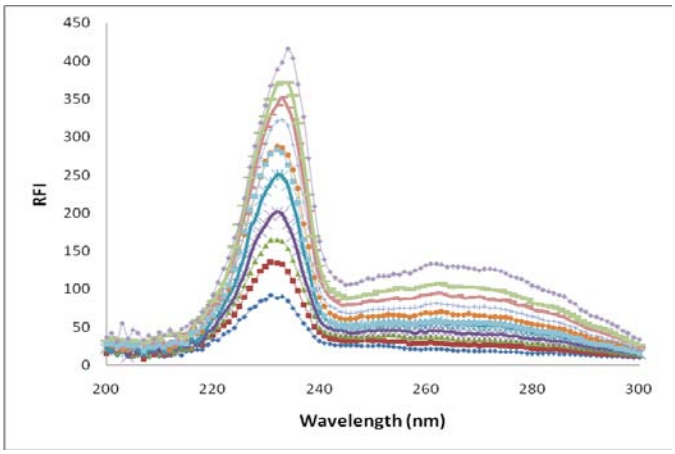

Fig. 6: Calibration of SUM using the proposed synchronous method using, (Δλ= 120 nm) in methanol with SLS added, the concentration range is (50-150 ng/ml)

Limit of detection (LOD) and limit of Quantitation (LOQ)

LOD and LOQ were calculated according to ICH Q2 (R_1) recommendations [ICH Expert Working Group. ICH harmonized tripartite guidelines. Validation of Analytical procedures: text and methodology [28], using the following equations and the results are shown in table 1

LOD = 3.3 Sa/b

LOD = 10 Sa/b

Where Sa: standard deviation of the intercept and Sb: standard deviation of the slope of the calibration curve.

Validation of the developed spectrofluorimetric methods

Table 1: Analytical Performance data of the proposed method

Parameter	SUM
Synchronous scanning range (nm)	200-300
Δλ (nm)	120
Linearity range (ng/ml)	50-150
Correlation coefficient	0.992
Slope (b)	0.939
Intercept (a)	68.4
SD of the intercept (Sa)	4.65
SD of the slope (Sb)	0.0021
% RSD[a]	1.3
LOD[b] (ng/ml)	16.3
LOQ[c] (ng/ml)	49.5

[a]Percent relative standard deviation of three replicate samples, [b]Limit of detection, [c]Limit of quantitation

Accuracy and precision

To investigate the accuracy and precision of the developed method, the assay results of SUM were compared from standard reference method [28], statistical analysis of the results using student's t-test and variance ratio *F*-test [30] showed no significant differences between the performance of the proposed method and reference method regarding accuracy and precision (table 2)

Table 2: **Assay results of the proposed method for SUM in pure and tablet forms compared with a reference method**

Parameter:	Proposed method		% Found	Reference method		% Found
	Amount taken (ng/ml)	Amount found (ng/ml)		Amount taken (ng/ml)	Amount found (ng/ml)	
	5.0	4.974	99.48	5.0	4.910	99.20
	10.0	9.876	98.60	10.0	10.074	100.27
	20.0	20.143	100.7	20.0	19.948	99.74
	50.0	49.651	99.30	50.0	50.204	100.41
*$\bar{x}$±SD			99.52±0.87			99.82±0.61
t-value	0.32					
F-value	0.57					
Oratab®						
100 mg tablet	20.0	19.93	99.6	20.0	20.07	100.4
	40.0	39.76	99.4	40.0	39.89	99.7
	60.0	58.85	98.3	60.0	59.87	99.8
*$\bar{x}$±SD			99.1±0.7			99.9±0.38
t-value 0.065 (3.18)						
F-value 0.450 (9.55)						

*mean±SD, (SD)-standard deviation, n=3, Numbers in the parentheses are the critical tabulated values of t and F at (P=0.05)

Table 3: Intra-assay and inter-assay precision and accuracy of the determination of SUM in tablets using the proposed method

Intra-assay			Inter-assay		
Nominal conc	**Measured conc.**	**Recovery conc**	**Nominal**	**Measured conc.**	**Recovery[a]**
(ng/ml)	(ng/ml)	(%±RSD)	(ng/ml)	(ng/ml)	(%±RSD)
50	50.23	100.5	50	49.65	99.3
100	99.68	99.7	100	97.86	97.9
150	149.57	99.7	150	147.83	98.6
[a]Mean of three determinations					
$\bar{x}$±SD		99.9±0.46		98.6±0.7	

Pharmaceutical applications

The developed method was successfully applied for the intra-day and inter-day determining (SUM) in its drug tablets on three successive days, the recovery results were obtained for the assay of SUM in pharmaceutical tablets as shown in (table 3). The results were comparable with those obtained from the reference method.

CONCLUSION

In this study, a new nonexpensive and sensitive procedure was developed for the determination of sumatriptan succinate based on the enhancement of native fluorescence of the studied drug using methanol as solvent and sodium lauryl sulfate as a micellar medium. The new method utilized the use of synchronous scanning for the determination of SUM in both pharmaceutical tablets, the method was validated and compared with reference methods.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICTS OF INTERESTS

Declared none

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