Research Article

SIMULTANEOUS ESTIMATION OF SUMATRIPTAN SUCCINATE, NAPROXEN AND DOMPERIDONE BY REVERSE PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A simple, accurate and precise reverse phase high performance liquid chromatography (RP-HPLC) method has been developed and validated for simultaneous estimation of sumatriptan succinate, domperidone and naproxen in bulk drugs as well as in pharmaceutical formulations. Chromatographic analysis was carried out on a LichroCART, C-18 column (250mm×4.6mm, 5μ), in isocratic mode. The mobile phase constituted of phosphate buffer: acetonitrile: methanol (40: 10: 50) and pH adjusted to 3.5 with dilute orthophosphoric acid and was delivered at certain flow rate programming. Detection was performed via programmed wavelengths at 280 and 262 nm. Calibration curves were linear over concentration range of 0.9 to30 μg/ml for the selected drugs and the correlation coefficients were found to vary between 0.99 to 1.0. The calculated intra-day and inter-day coefficients of variation were found to be less than 5%. .

Keywords: Migraine, Sumatriptan succinate, Domperidone, Naproxen, RP-HPLC.

INTRODUCTION

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side which comes in attacks lasting 4-48 hours and is often associated with nausea, vomiting, sensitivity to light and sound and other symptoms. Migraine is of two types- with _aura_ (classical) in which headache is preceded by visual or neurological symptoms and migraine without _aura_ (common migraine)[1]. Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patient to various drugs determine the choice. Sumatriptan succinate, domperidone and naproxen are widely used for the treatment of migraine with aura either as monotherapy or as multiple drug therapy for better efficacy.

Sumatriptan stimulates 5-HT receptors of the 1D subtype, resulting in selective vasoconstriction of inflamed and dilated cranial blood vessels in the carotid circulation. It also blocks the release of vasoactive neuropeptides from perivascular trigeminal axons in the duramater during migraine[2]. Sumatriptan is indicated for the acute treatment of migraine attacks with or without aura.

Domperidone has peripheral dopamine receptor (D_1 and D_2) blocking properties which increase gastric motility and peristalsis, therefore, facilitating gastric emptying and decreasing small bowel transit time. It is used in GI motility disorders[3]. Besides this, it is also prescribed for management of emesis in antimigraine therapy.

Naproxen works by inhibiting both isoforms of enzyme cyclooxygenase i.e. COX-1 and COX-2. Inhibition of COX-1 is thought to be associated with gastrointestinal and renal toxicity while inhibition of COX-2 provides anti-inflammatory activity[4]. Naproxen is useful in case of various painful inflammatory conditions like rheumatoid arthritis, osteoarthritis and dysmenorrhoea.

A combination of sumatriptan succinate and naproxen (Treximet®) has been approved by Food and Drug Administration (FDA) as fast disintegrating tablet[5]. Analytical methods available for determination of sumatriptan succinate include electrochemical detection[6], LC-MS-MS[7], liquid chromatography detection by UV[8-9]. Domperidone can be analysed through UV spectrophotometry[10-11] and HPLC[9,12]. Analytical journals report the estimation of naproxen through liquid chromatography[13-14]. Among these methods, HPLC is an accurate and precise method for estimation of drugs in bulk and their formulations. Various workers have reported HPLC methods for individualistic estimation of sumatriptan, naproxen and domperidone with few reports of simultaneous estimation of any two drugs from these three. Simultaneous estimation of two or more drugs by reverse phase high performance liquid chromatography (RP-HPLC) is also common in literature [15]. However, there is no HPLC method for sumatriptan, nonsteroidal antiinflammatory drugs

(NSAIDs) and antiemetics in triple combinations[16]. In the present study, an attempt has been made to include an antiemetic drug, domperidone with sumatriptan and naproxen, since antimigraine therapy often includes drugs for management of emesis. The molecular structures of these drugs are shown in Figure 1.

a) Sumatriptan succinate

b) Domperidone
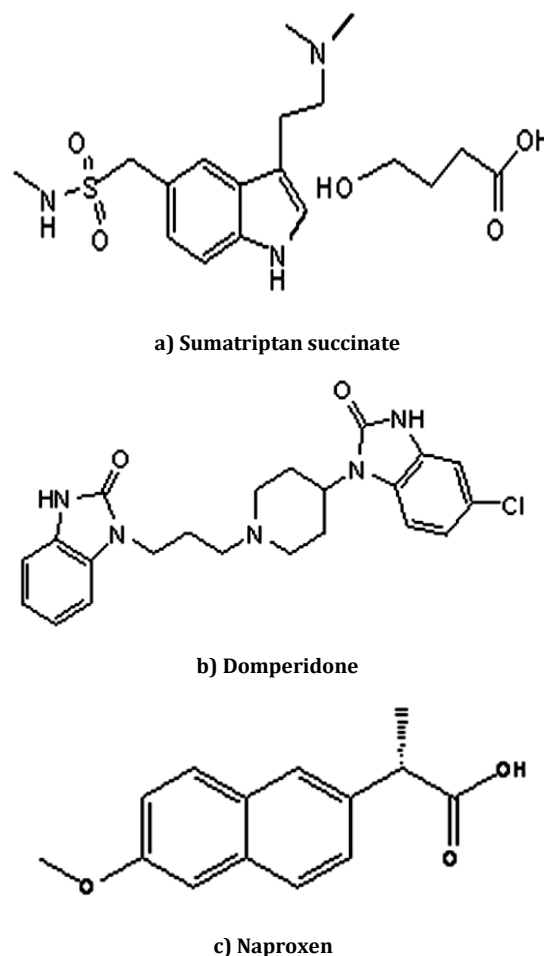
c) Naproxen

Fig. 1: The molecular structures of a) Sumatriptan succinate, b) Domperidone and c) Naproxen

EXPERIMENTAL

Instrumentation

Analysis was carried out using Shimadzu HPLC system coupled with SPD-10 AVP (UV/Vis Detector) on a LiChroCART® C-18 column (250mm×4.6mm) packed with 5µ particle size as stationary phase. The pump used was solvent delivery module LC-10AT$_{VP}$ (double reciprocating plunger type) and a Rheodyne injector with 20 µL loop was used for injecting sample. The detection was carried out using (SPD-10A VP) UV detector set at wavelength programming.

Drugs and Chemicals

Sumatriptan succinate was procured from Ranbaxy Research Labs, Gurgaon (India); domperidone from Symbiotic Drug and Diabetic Care, Baddi (India) and naproxen from Unicure Pvt. Ltd, Noida (India) as gift samples. HPLC grade acetonitrile, methanol and potassium dihydrogen phosphate were procured from SD Fine Chem. Ltd., India and orthophosphoric acid from Merck Ltd., India. HPLC grade water was prepared using Millipore Direct ® Q$_3$ ultra filtration unit.

Preparation of solutions

The mobile phase, 40mM, potassium dihydrogen orthophosphate - acetonitrile - methanol in the ratio of 40: 10: 50, pH 3.5 was delivered in isocratic mode at certain flow rate programming.

Preparations of Standard Stock Solutions

10 mg of individual drug was accurately weighed and transferred to a 10 ml volumetric flask separately and dissolved in diluting solution (acetonitrile : methanol : water, 35:35:30) to make volume up to 10 ml (1000 µg/ml standard stock solution) individually for selected drugs. 1 ml of above solution was transferred into 10 ml volumetric flask and volume was made up to 10 ml with diluting solution (100 µg/ml working stock solution).

Preparation of Calibration Curves

For making standard calibration curve, 30 µg/ml dilution was prepared from 100 µg/ml working stock solutions of sumatriptan succinate, domperidone and naproxen separately. Serial dilutions ranging from 0.9 to 30µg/ml were prepared and injected to obtain a chromatogram for each drug.

Preparation of Quality control standards

Three quality control standards of high, medium and low concentrations (30µg/ml, 7.5µg/ml and 1.87µg/ml) of standard mixture solution were prepared, injected and obtained HPLC data were compared with the standard calibration curve.

Analysis of tablet formulation

Accurately weighed sample (weight equivalent to one tablet) was placed directly into a graduated flask with diluting solution (acetonitrile: methanol: water, 35:35:30) followed by stirring on magnetic stirrer for 30 minutes. The resulting solution was then diluted by measured volume of diluting solution to prepare 1000 µg/ml stock solution. The stock solution was centrifuged for 15 minutes at 5000 r.p.m. Subsequent dilutions were made with solvent mix in order to obtain 100µg/ml working stock solution. In order to confirm the validity of the developed method, quality control concentrations for tablet sample were analyzed. Obtained HPLC data was compared with the standard calibration curve. The amount of drug present in the tablet sample solution was calculated by linearity equation of standard calibration curve.

RESULTS AND DISCUSSION

Chromatography

The chromatogram of best resolution and minimum tailing was obtained by RP-HPLC method using 40mM, 3.5 pH, potassium dihydrogen ortho phosphate - acetonitrile - methanol (40: 10: 50, v/v) as mobile phase. The retention time (R.T) for sumatriptan succinate, domperidone and naproxen in optimized conditions was

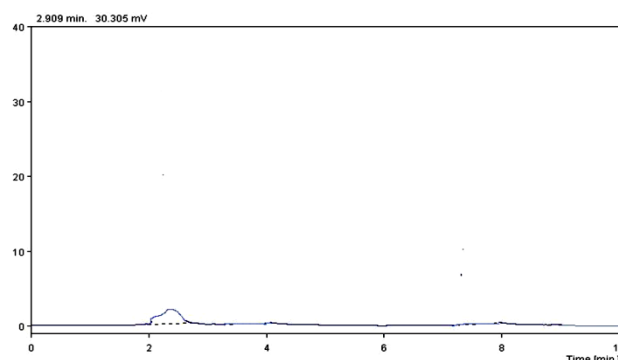observed to be 2.2, 3.7 and 7.9 min respectively. The chromatograms are shown in Figures 2 and 3.

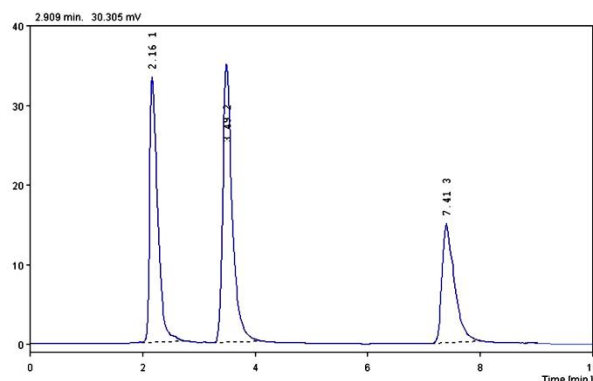
Fig. 2: Chromatogram of drug free mobile phase

Fig. 3: Standard chromatogram of sumatriptan succinate (R.T 2.16 min), domperidone (R.T 3.49) and naproxen (R.T 7.41)

METHOD VALIDATION

Linearity and Calibration standards

The least square regression analysis was performed on peak area of each drug versus its nominal concentration in the range of 0.9-30 µg/ml and correlation coefficient was found to be 0.99 to 1.00. A linear relationship was observed for all drugs as shown in Table 1.

Table 1: Regression equation and correlation coefficient (r²)

Drug	Regression equation	r^2	LOD (ng/ml)	LOQ (ng/ml)
Sumatriptan succinate	y = 24.182 x + 7.4242	0.9998	65.83	219.45
Domperidone	y = 27.11 x + 1.2372	1.0	26.35	87.85
Naproxen	y =14.472 x + 1.6287	1.0	61.87	206.25

Specificity

The specificity studies revealed the absence of any other excipient interference, since not a single peak of excipient appeared at the same retention time of sumatriptan succinate, domperidone and naproxen in the chromatogram, as shown in Figure 3.

The interaction study between the three drugs in the standard solution was carried out by comparing peaks of each drug individually with peaks obtained in drug mixture indicating that the analytes did not interact with each other and data were within the acceptance level of ±2.0%.

Accuracy and Precision

The precision and accuracy of method were determined and calculated as % relative standard deviation (RSD) or % coefficient of variance (C.V) and % Bias respectively. The values of % C.V, % Bias in Table 2 show that the method is accurate within the acceptable limit of 2%.

LOD and LOQ

For determining the limit of detection (LOD) and limit of quantitation (LOQ), the method based on standard deviation and slope was adopted. The values obtained are highlighted in Table 3.

Table 2: Intra-day and inter-day accuracy and precision data of Sumatriptan succinate Domperidone and Naproxen

Spiked Conc. (µg/ml)	Intra-day		Inter-day	
	Precision %CV	Accuracy %Bias	Precision %CV	Accuracy %Bias
Sumatriptan succinate				
1.87	0.42	-1.87	0.57	-2.9
7.50	2.84	-1.3	2.50	-2.6
30.00	1.09	-1.3	1.32	-1.6
Domperidone				
1.87	2.94	+1.3	2.19	+1.3
7.50	2.52	+2.6	2.87	+2.6
30.00	0.8	-1.0	1.42	-1.6
Naproxen				
1.87	1.63	+1.3	1.26	-3.5
7.50	1.97	-1.3	2.33	+1.3
30.00	1.33	0.0	1.41	-1.0

Table 3: LOD and LOQ of drugs

Drug	LOD (ng/ml)	LOQ (ng/ml)
Sumatriptan succinate	65.83	219.45
Domperidone	26.35	87.85
Naproxen	61.87	206.25

Stability

Sumatriptan succinate, domperidone and naproxen were found to be stable for all validation parameters observed at 48 hours interval for fourteen days since no extra peak as well as no deviation in original peak area was observed. % C.V. of quality control samples was found to be less than 5%.

Analysis of Tablets

The value of analysis of tablets obtained by the proposed method were between 97.86 to 101.09%, which showed that the estimation of dosage forms were accurate within the acceptance level of 95-105%. The values obtained are highlighted in Table 4.

Table 4: Estimation of three drugs in mixture of tablets

Drug	Quantity claimed (mg/tab)	Quantity found (mg/tab)	% quantity found (±SD)
Sumatriptan Succinate	25 mg	24.466	97.86 (±0.534)
Domperidone	10 mg	10.109	101.09 (±0.109)
Naproxen	250 mg	249.855	99.94 (±0.145)

System suitability parameters

System suitability parameters as retention time, peak asymmetry, capacity factor and resolution were calculated from data obtained from three replicate injections of mixed standard solutions to check the system performance. The results are presented in Table 5.

Table 5: System suitability data of developed method

Factors	Sumatriptan	Domperidone	Naproxen
Retention time (min)	2.21	3.71	7.91
Peak asymmetry	1.714	1.526	1.652
Capacity factor	1.21	2.59	6.55
Resolution	-	5.490	17.918

CONCLUSION

A sensitive, specific and validated RP-HPLC assay is described for simultaneous estimation of drugs used in antimigraine therapy i.e. sumatriptan succinate, domperidone and naproxen. The amounts of drugs obtained lie between 97.86% and 101.09% within acceptance level of 95% to 105%. This method is also useful for analysis of individual drug or combination of any two drugs out of proposed drugs. Hence, the present method is cost effective and adaptable to routine analysis. Since this method is simple, rapid, accurate, sensitive and specific, it could therefore be used for analysis in biological specimens.

ACKNOWLEDGMENTS

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