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Development and Validation of a Stability Indicating UV-Spectrophotometric Assay Method for the Determination of Naratriptan Hydrochloride

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ABSTRACT

The research in this paper discusses about the development and validation of a novel, cost effective, simple, reproducible and accurate UV-spectrophotometric method to estimate naratriptan hydrochloride in bulk as well as pharmaceutical formulations. Naratriptan hydrochloride was analyzed at 223 nm in simulated saliva (pH 6.8) and phosphate buffer (pH 7.4). Linearity was present in the concentration range of 1–40 µg/ml for both media. The method was validated as per different parameters according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines of Q2 (R1). The suggested method was successfully used for the analysis of naratriptan hydrochloride in-house oral film formulation as linearity values for the same were found to be 1–40µg/mL. The results revealed the suitability of the technique for the estimation of naratriptan hydrochloride in the oral films for its accuracy, precision, and reproducibility.

Keywords: ICH, Naratriptan hydrochloride, phosphate buffer, Q2 (R1), simulated saliva, UV-spectrophotometric

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INTRODUCTION

2-[3-(1-Methyl-piperidin-4-yl)-1H-indol-5-yl]-ethanesulphonic acid methylamide hydrochloride or also known as Naratriptan hydrochloride is a serotonin 5-$HT_{1B/1D}$ receptor agonist. The chemical structure of naratriptan hydrochloride is as per shown in Figure 1.

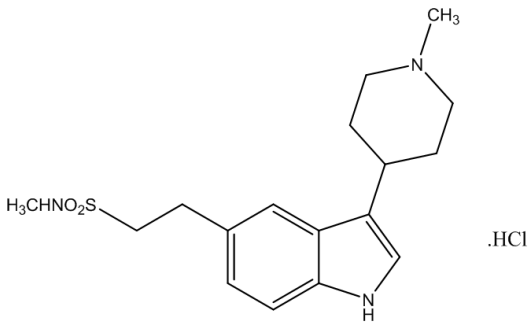

Figure 1. Chemical structure of naratriptan hydrochloride

It is a serotonin 5-$HT_{1B/1D}$ receptor agonist and used for the treatment of acute migraine. Activation of 5-HT_{1B} receptor, which is present on the vascular smooth muscles, causes vasoconstriction of smooth muscles (Longmore, et al., 1997). 5-HT_{1D} receptors are located on the sensory trigeminal terminals. Activation of these receptors inhibits the release of sensory and vasoactive neuropeptides as well as vasodilator transmitters (Reuter et al., 2002; Saxena et al., 2018).

Acute migraine is a disabling disorder characterized by moderate to severe throbbing and pulsating pain often associated with phonophobia, photophobia, nausea, and vomiting. It worsens with day to day activity of patient (Goadsby, 2003; Vecchia & Pietrobon, 2012). An untreated migraine attack can last for 4 to 72 hours (Tepper & Spears, 2009; Skaer, 2018). Migraine can also cause sexual dimorphism i.e. prevalence ratio among men and women is 3:7 (Estemalik & Tepper, 2013) (Dhillon et al., 2011).

The suggested analytical method will be beneficial since few have been reported in the literature for the proposed drug. This method analyzes the drug sample by using UV spectrophotometer. The observation of analysis and the method validation data confirms the reproducibility of the method. The novelty of this work lies on the broad linearity and lower standard deviation values as compared to previous work done (Sreelakshmi et al., 2013; Borse & Shirkhedkar, 2012; Shelke, 2015).

MATERIALS AND METHODS

Materials and Reagents

Naratriptan hydrochloride was obtained as a gift sample from Apotex Pharmachem Pvt. Ltd., India. The oral film formulations contain 5 mg of proposed drug per film and was

formulated in-house. The polymers used were hydroxyl propyl methyl cellulose (HPMC) E5 and propylene glycol in the formulation along with other excipients obtained from SD-Fine Chemicals, India. All other chemicals such as dibasic sodium phosphate, disodium hydrogen phosphate, monobasic sodium phosphate, sodium chloride and HCl used in the method were of Analytical Grade (AR) obtained from LOBA Chemie, India.

Instruments

A double beam UV-visible spectrophotometer (U-2900/U-2910 Shimadzu Co. Ltd., Japan) provided with UV-Probe software was used. For intermediate precision studies, another UV-visible spectrophotometer (SL 159 Elico Ltd., India) was used. Automatic wavelength accuracy check was previously performed on both instruments, which was found to be 0.1 nm and provided with matched quartz cells of 1.0 cm cell path length.

Method Development

Analysis of the proposed drug formulations was performed in various media. The criterion for the selection of specific media was the solubility of the drug, cost of solvents, sensitivity of the method, applicability and method robustness (Verma et al., 2014).

Preparation of Simulated Saliva (pH 6.8). Weighed amounts of dibasic sodium phosphate (0.19g), disodium hydrogen phosphate (2.38g), and sodium chloride (8g) were put in a 1000-ml capacity volumetric flask and dissolved in a small amount of distilled water. The volume was made up to 1000 mL with distilled water. The pH was adjusted to 6.8 by using NaOH and HCl.

Preparation of Phosphate Buffer (pH 7.4). Weighed amounts of monobasic sodium phosphate (2.62g) and dibasic sodium phosphate (11.50g) were taken and dissolved in distilled water. The final volume was made up to 1000 ml with distilled water. The pH was adjusted to 6.8 by using NaOH and HCl (India et al., 1985).

Procedure for Calibration Curve. Naratriptan hydrochloride (10mg) was dissolved in 100 ml of phosphate buffer (pH 7.4) and simulated saliva (pH 6.8) to prepare a stock solution of 100µg/ml concentration. Standard volumetric flasks were used to form dilutions of six different concentrations in the range of 2-12 µg/ml in phosphate buffer (pH 7.4) and 1-10 µg/ml in simulated saliva (pH 6.8) for a calibration curve. Samples were analyzed for both solutions at 223 nm.

Sample Preparation. The film formulation of the proposed drug was dissolved in each medium separately. Suitable dilutions were done to get final concentration of 5µg/ml and filtered through nylon filters.

Validation of Developed Analytical Method (Guideline, 2005)

Specificity. Naratriptan hydrochloride solution (5µg/ml) in both media and placebo solutions were scanned in the range of 400 to 200 nm to analyze the absorbance shift at the respective wavelength. The standard deviations were determined after making out comparison of above results.

Accuracy. For determination of accuracy, three levels of API concentrations i.e. higher concentration (HC), intermediate concentration (IC), and lower concentration (LC) were prepared from stock solution and analyzed (n = 3). The mean, standard deviation (SD), percentage relative standard deviation (RSD) were calculated at each level. The overall SD, overall percentage RSD, and compiled percentage recovery were also calculated from the data.

Precision. Different drug concentrations were analyzed for repeatability studies. Determinations of Inter-day, inter instrument variation and intra-day were carried out to find the intermediate precision. Intra-day and inter-day variation were determined to analyze the samples at three different times periods per day and three different days respectively. Same procedure was followed for inter-instrument variations and samples were re-analyzed using a U-2900/U-2910 Shimadzu Co. Ltd., Japan. (n = 3).

Linearity. For determining linearity, six concentrations ranging 1–10µg/mL of the proposed drug were prepared from the stock solution and least square regression analysis was employed.

Robustness. Proposed method was analyzed for robustness by: (a) changing wavelength maxima by ±5 nm i.e. 228 nm and 218 nm and (b) changing pH of the respective media by ±0.4unit.

RESULTS AND DISCUSSION

Method Development

Various media like water, 0.1N HCl, acetate buffers (pH4.5), simulated saliva (pH 6.8) and phosphate buffer (7.0-10.2) were investigated for optimization of the medium. On the basis of outcomes simulated saliva (pH 6.8) and phosphate buffer (pH 7.4) were finally selected as the suitable media. The spectra of naratriptan hydrochloride in both media were determined and λ_{max} was found to be 223 nm (Figure 2).

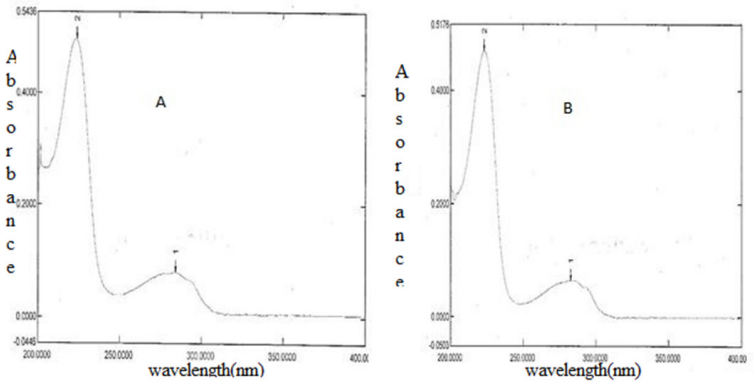

Figure 2. UV spectra of naratriptan hydrochloride in simulated saliva pH 6.8 (A) and phosphate buffer pH 7.4 (B)

Calibration Curve

The linear regression equations were obtained at 223nm, (0.0991 × concentration in µg/ml) + 0.0534, with a regression coefficient of 0.9982 and (0.0882 × concentration in µg/ml) - 0.0006, with a regression coefficient of 0.9962 for simulated saliva (pH 6.8) and phosphate buffer (pH 7.4) respectively (Figure 3).

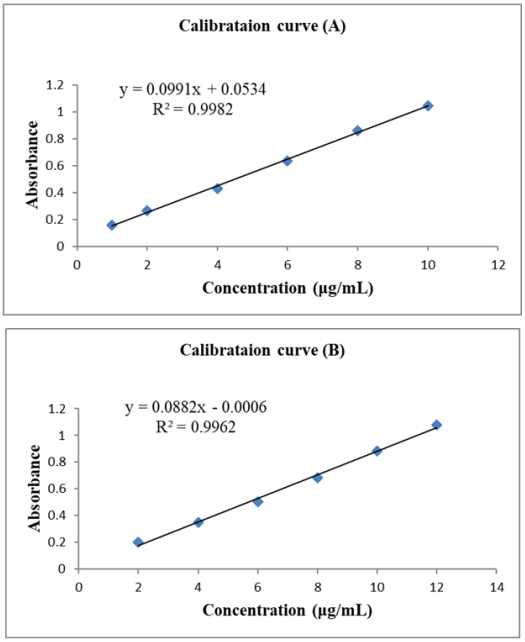

Figure 3. Calibration curves of naratriptan hydrochloride in simulated saliva pH 6.8 (A) and phosphate buffer pH 7.4(B)

Validation of Developed Analytical Method

Specificity. Since the UV-spectrum of the proposed drug was similar for film in both media, (Figure 2) it was found that no major difference was observed between the mean absorbance. Also, no interference peaks were present in blank and placebo solutions on 223nm. Hence the proposed analytical method features specificity for naratriptan hydrochloride.

Accuracy. The percentage mean recovery values observed were close to 100%. The standard deviation values for overall recovery data were less than 1.41 for both medias. The observed standard deviation values for overall accuracy were less than 1.73 and 1.35 in simulated saliva pH 6.8 and phosphate buffer pH 7.4, respectively representing the higher accuracy of the proposed analytical method. In simulated saliva pH 6.8, the %RSD values for percentage mean recovery for higher, intermediate and lower drug concentrations levels were found to be 97.69, 101.02 and 98.61, respectively. In phosphate buffer pH 7.4, these values were found to be 96.98, 99.52 and 98.99, respectively (Table 1 and Table 2).

Table 1

Data for overall recovery in simulated saliva and phosphate buffer

Parameters	**Values**
Overall mean	98.90
Overall S.D.	1.41
Overall %RSD	1.43

Table 2

Accuracy data in simulated saliva and phosphate buffer

Parameters	**Values**		
Simulated saliva pH 6.8	Mean	S.D.	%RSD
Accuracy Level 1	97.69	0.42	0.53
Accuracy Level 2	101.02	1.05	1.06
Accuracy Level 3	97.69	0.52	0.43
Overall data for accuracy	99.11	1.71	1.73
Phosphate buffer pH 7.4			
Accuracy Level 1	96.98	0.47	0.43
Accuracy Level 2	99.52	0.34	0.34
Accuracy Level 3	98.99	0.43	0.49
Overall data for accuracy	98.50	1.33	1.35

Precision. Intermediate precision and repeatability were performed for sample concentration in simulated saliva pH 6.8 and phosphate buffer pH 7.4. The percent RSD were found to be less than 1 for both media (Table 3).

Table 3

Data for repeatability and intermediate precision in simulated saliva pH 6.8 and phosphate buffer pH 7.4

Parameters	Values		
	Mean	S.D.	%RSD
Repeatability*	0.54 (abs.)	0.002	0.40
Inter. precision*	99.41	0.47	0.47
Repeatability**	0.44(abs.)	0.002	0.55
Inter. precision**	99.72	0.82	0.82

* In simulated saliva pH 6.8; **in phosphate buffer pH 7.4

Linearity. The linearity of the analysis for the proposed drug was found to be 1–40µg/mL (r^2= 0.9864) and 1–40µg/mL (r^2 = 0.9901) in simulated saliva pH 6.8 and phosphate buffer pH 7.4, respectively. High precision of the proposed methods was confirmed from lower values of standard error (S.E.) and the mean slope and intercept values are within the 95% confidence interval (Table 4).

Table 4

Linear regression data for the linearity curve in simulated saliva (pH 6.8) (n = 9) (I) and in phosphate buffer (pH 7.4) (n = 9) (II)

Parameters	**I**	**II**
Correlation coefficient(r)	0.9978	0.9976
"r" squared	0.9958	0.9953
Slope	0.1015	0.0926
S.E. slope	0.0025	0.0024
95% confidence limit of slope	0.0955–0.1074	0.0870–0.0983
Intercept	0.0304	0.0312
S.E. Intercept	0.0092	0.0088
95% confidence limit of intercept	0.0087–0.0521	0.0105–0.0520

Robustness. It was found that small variation in the pH of the selected media i.e. ±0.4 did not have significant effect on the absorbance of the naratriptan hydrochloride. The percent mean recoveries (±S.D.) were found to be 98.70 (±1.75) and 98.99 (±0.53) in simulated saliva pH 6.8 and phosphate buffer pH 7.4.

Analysis of Oral Film Formulations

In simulated saliva pH 6.8, the measure estimations of drug for various formulations were in the range of 98.60% to 99.41% along with a standard deviation not more prominent than 0.42. In phosphate buffer pH 7.4 medium, these values were in the range of 97.64% to 99.22% along with a standard deviation not more than 0.81. The assay results of formulation were not having significant differences. This demonstrates that there is no significant effect of excipients for the estimation of naratriptan hydrochloride in the oral films by using the proposed method.

The above proposed analytical method is accurate, rapid, simple, inexpensive, and precise. Therefore, it can be used for the estimation of naratriptan hydrochloride in different dosage forms. The recoveries of naratriptan hydrochloride from formulation were found to be in good agreement with their respective claims for this API, which tells about there is no interference of formulation excipients which are present in the oral film. Moreover, this method is also very fast with respect to analysis time as compared to HPLC.

The %RSD values of all the parameters for the proposed analytical method for the analysis of naratriptan hydrochloride are lying between 0.34 – 1.06 as these are lesser as compared to previous work.

CONCLUSION

The above proposed analytical method is accurate, rapid, simple, accurate, inexpensive, and precise. Therefore, it can be used for the estimation of naratriptan hydrochloride in different dosage forms.

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