International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 05, 2020
ISSN: 1475-7192

Investigation of Ketotifen Fumarate in Pharmaceuticals Using Iron (III) Chloride and Two Chelating Agents – Spectrophotometerically

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Abstract--- *Spectrophotometric methods for the drug, ketotifen fumarate (KTF) have been developed and validated both for bulk drug and its tablets by two simple, selective methods. This involves oxidation of KTF with ferric chloride in neutral medium and successive chelation of the resulting iron (II) with 1, 10-phenanthroline (phen) (Method A) or 2, 2′-bipyridyl (bipy) (Method B). The resultant red colored chromogens are measured at 510 for method A and 520 nm for method B. Beer's law is obeyed in the concentration ranges of 0.4-8.0 and 1-25 μg ml-1 with molar absorptivity values of 5.35 x 104 and 0.789 x 104 l mol-1cm-1 and Sandell sensitivities 0.008 and 0.055 μg cm-2 for method A and method B, respectively. The limits of detection and quantification are also stated. For the present paper, the proposed methods were applied for the determination of KTF. There was a good comparison of the results for proposed procedures and the reference method, no much difference in accuracy and precision.*

Keywords--- *Spectrophotometry, Ketotifen Fumarate, Pharmaceuticals.*

I. INTRODUCTION

Ketotifen fumarate (KTF), chemically known as 4,9-Dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5] cyclohepta-[1,2-b] thiophen-10-one (Figure 1), an antiallergic drug with stabilizing action of mast cells, similar to sodium cromoglycate [1]. Ketotifen is orally given as fumarate in management of asthma and is used to treat of allergic conditions [2]. Also is a nonbronochodilator, has antiallergic properties [3].

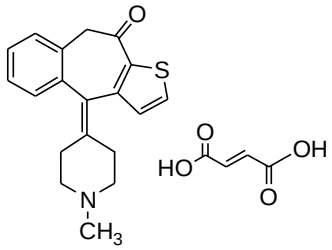

Figure 1: Structure of KTF

The officially established drug in British Pharmacopoeia [4], explains a potentiometric titration with perchloric acid. The positivity of the drug has provoked the development of a variety of procedures for it's analyze in pharmaceuticals, also body fluids. In pharmaceuticals, it is quantified by chromatography method[5–12], chromatography using tandem mass spectrometry [13], capillary electrophoresis [14], spectrofluorimetry [15**], pulse polarographic and voltammetry [16], UV-spectrophotometry [17,18]. P**olymeric membrane as sensors were

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DOI: 10.37200/IJPR/V24I5/PR2020680
Received: 16 Apr 2020 | Revised: 22 Apr 2020 | Accepted: 12 May 2020

used which involved potentiometric titration of the KTF with sodium tetraphenylborate [19, 20]. Chemiluminescene [21-23] method, Coulometric titration [24] based reactions were carried out for KTF determination. Due to ease of operation, cost-effectiveness, precision, sensitivity, fair wide applicability and accuracy, visible spectrophotometry serve as an useful alternative.

Several spectrophotometric studies including the amino or thiophene of the ketotifen molecule can be found in the literature study. Kousy and Babawy [25] have developed a method based on extraction of drug-cobalt thiocyanate ternary complex. Sastry and Naidu [26] have determined the drug in tablets and syrup based on the reduction method. Literature shows the use of ion-pair reaction for the assay of KTF using azocarmineG as ion- pair reagent at pH 1.5 where the ion- pair complex extracted into $CHCl_3$ and absorbance measured at 540 nm [26]. An ion-pair complex formation with bromocresol green by the drug determined by spectrophotometrically [27, 28] at pH 3.0 followed by its extraction in chloroform and absorbance measured at 423 nm. Vachek [29] assayed KTF by a charge–transfer reaction with picric acid, which involved extraction of the picric acid-drug complex into chloroform and measurement at 405 nm. The procedures involved oxidation of KTF with iron (III)chloride and determining the resulting iron (II) by complexing with either 1, 10-phenanthroline (Method A) or 2, 2′-bipyridyl (Method B). The complex formation of Fe^{2+} with 1, 10-phenanthroline **[30]** and 2, 2′-bipyridyl**[31-33]** has long been recognized. Simplicity, sensitivity, wide linear dynamic ranges, mild experimental conditions and above all cost-effectiveness characterize the proposed methods.

II. EXPERIMENTAL

The absorbance was measured using a Systronics model 106 digital spectrophotometer with 1-cm matched quartz cells.

A. Materials and Reagents

All AR grade reagents and double-distilled water preferred in the current study. Pharmaceutical grade KTF (99.78 per cent pure) was purchased from Cipla India, Ltd., Mumbai. Asthafen-1(Torrent pharmaceuticals, Sikkim, India,) and Ketasama-1 (Sun pharmaceuticals, Sikkim, India) tablets were purchased.

Other reagents prepared:

B. Ferric Chloride (Hydrated, 3mM)

The stock solution of 0.05 M ferric chloride prepared by dissolving 1.35 g in 100 ml of water and stored in a dark bottle. The stock solution was then suitably diluted with distilled water to get working concentration for both methods. The solution was prepared afresh just before the experiment.

C. 1,10-phenanthroline (0.01 M)

The solution was set by dissolving 198 mg of 1,10-phenanthroline in distilled water and diluted to 100 ml with distilled water.

D. 2,2’-Bipyridyl (0.01 M)

E.. Orthophosphoric acid (0.02 M)

DOI: 10.37200/IJPR/V24I5/PR2020680
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III. General Procedures

A. Method A (Using 1, 10-Phenanthroline)

0.2, 0.5, 1.0, 2.0, 3.0 and 4.0 mL of the standard 20 μg mL^{-1} KTF solution pipetted into a series of 10 mL standard flasks and the total volume adjusted to 4 mL by adding distilled water. To each flask, added 2 mL of ferric chloride and 2 mL of 0.01 M 1,10-phenanthroline, 1 mL of orthophosphoric acid, and the total volume made to 10 mL . The content was shaken, and kept as such for 10 min. Later, measured the absorbance of each solution at 510 nm.

B. Method B (Using 2, 2´-Bipyridyl)

0.2, 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mL of KTF solution (50 μg mL^{-1}) was measured into 10 mL calibrated flasks with help of a micro-burette and made up to 5 mL by water. To this added 2 mL of 3 mM ferric chloride, 2 mL of 0.01 M 2,2'-bipyridyl and 1 mL of orthophosphoric acid (0.02 M). The content shaken well after diluting to the mark with double distilled water. At 520 nm the absorbance of each solution was measured. Graph was plotted between absorbance values vs concentration of KTF (μg mL^{-1}).

C. Procedure for Tablets

10 mg of KTF tablet was weighed and taken into a 100 ml flask, 60 ml of water added and shaken for 15-20 min to extract the drug into the liquid phase; later diluted up to the mark, mixed well and using Whatman No. 42 filtered. 20 and 50 μg ml^{-1}concentrations of the filtrate taken for Method A and Method B, respectively.

D. Placebo Blank Analysis

Composition: Starch (20 mg), talc (15 mg), acacia (30 mg), methyl cellulose (25 mg), sodium citrate (20 mg), sodium alginate (30 mg), and magnesium stearate (25 mg).

E. Procedure for the Determination of KTF in Synthetic Mixture

10 mg of KTF added to the placebo blank of the composition given above, transferred to a 100 ml flask. Working concentrations of 20 and 50 μg ml^{-1} in KTF were collected for Methods A and Method B, respectively. These analysis studied the interference talc, starch, acacia, methyl cellulose, sodium alginate, sodium citrate and magnesium stearate.

IV. Result and Discussion

The drive of this study was to launch simple spectrophotometric methods for the assay of KTF in pure form and in its pharmaceutical dosage forms. KTF contains a sulphur group, which could be oxidized to sulfoxide group and the drug was found to undergo oxidation with $FeCl_3$ in neutral medium. The complex formation of Fe^{2+} with 1, 10-phenanthroline and 2, 2´-bipyridyl has long been recognized. The proposed methods involved two steps:

The first step is the oxidation of KTF with excess $FeCl_3$ in neutral medium, and the second step is the determination of the resulting Fe^{2+} by subsequent chelation with either phen or bipy and measuring the absorbance at the respective wavelength (Figure 2). (Scheme 1). The amount of Fe^{2+} formed was found to be proportional to the amount of KTF serving as basis for its quantification. KTF consumes Fe^{3+}, and thereby Fe^{2+} concentration increases.

DOI: 10.37200/IJPR/V24I5/PR2020680
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This is observed as a proportional increase in the absorbance of the colored species with increasing concentration of KTF and fixed concentration of reagent. Graph was plotted for absorbance values at 510 nm in Method A and at 520 nm in Method B against the concentration of KTF to find the calibration graph.

A. Optimization of the reaction conditions

The quantitative determination of KTF was done to obtain maximum color development. When the [Fe^{3+}] was increased, the absorbance value of reagent blank was found to increase. Considering the sensitivity with a minimum blank absorbance, 2 ml of 3 mM ferric chloride in 10 ml were found optimum in Method A and Method B and used throughout the experiment. Even though, oxidation of KTF by Fe^{3+} and subsequent chelation of Fe^{2+} with either Phen or Bipy was found to occur in neutral medium, the presence of *o*-phosphoric acid was necessary to increase the stability of the developed red color chelate by maintaining the desired pH. A 1 ml of 0.02 M O-phosphoric acid in a total volume of 10 ml was found adequate in both the methods. Several experiments were carried out to study the effect of Phen and Bipy concentrations on the color development. To determine the optimum concentration of Phen, different volumes (0.5-2.5 ml) of 0.01 M Phen solution were used with a constant concentration of KTF (6 µg mL^{-1}) in a total volume of 10 ml and 1.5-2.5 ml of Phen solution was found to give persistent absorbance values. Hence, 2 ml of Phen solution in a total volume of 10 ml is static (Figure 3). In Method B, 2 ml of 0.01 M Bipy solution in 10 ml was found to give the maximum absorbance values (Figure 3), hence, the same volume was used. The standing times for full color development were found to be 10 min for both methods; and the color was stable for 30 min thereafter in both methods.

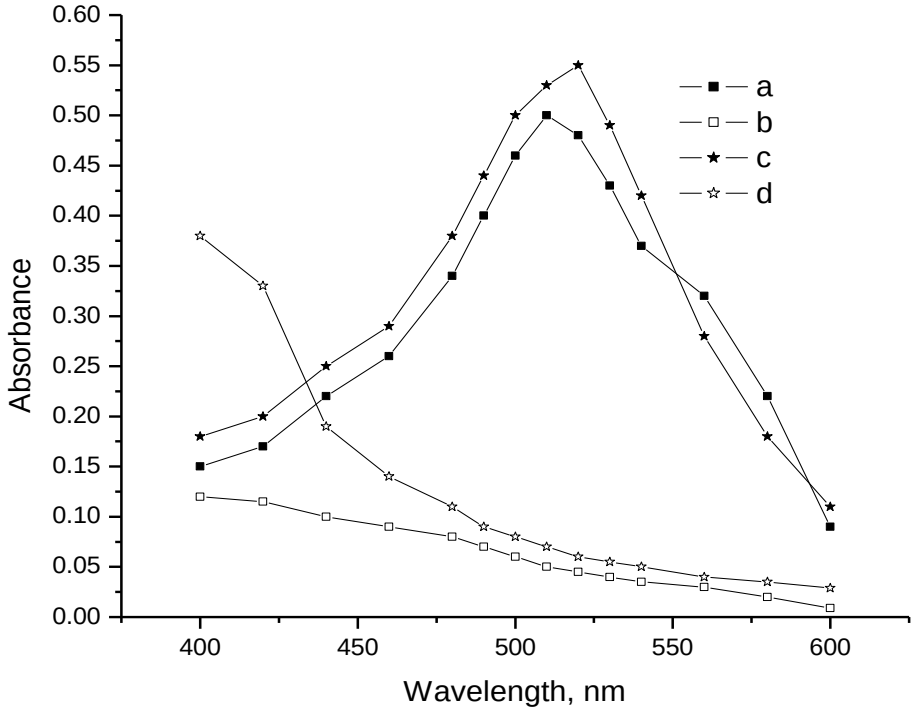

Figure 2: a-Fe(II)-phen complex, b-blank (Method A) c-Fe(II)-bipy complex and d-blank (Method B)

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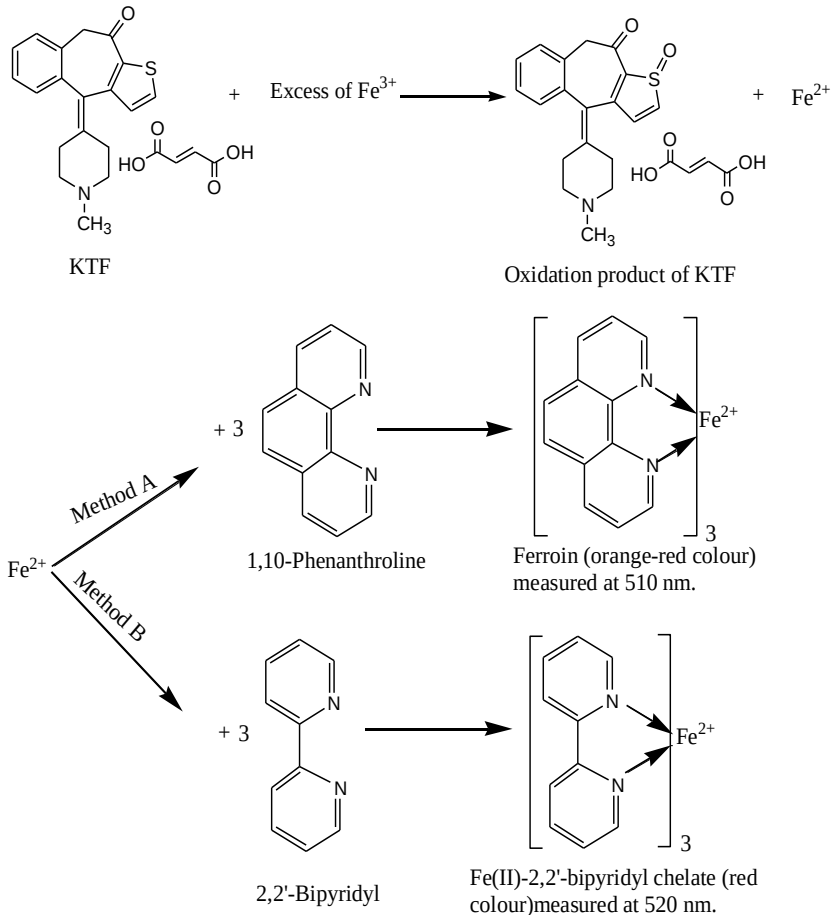

Scheme 1: Possible Reaction Pathway for the Proposed Methods

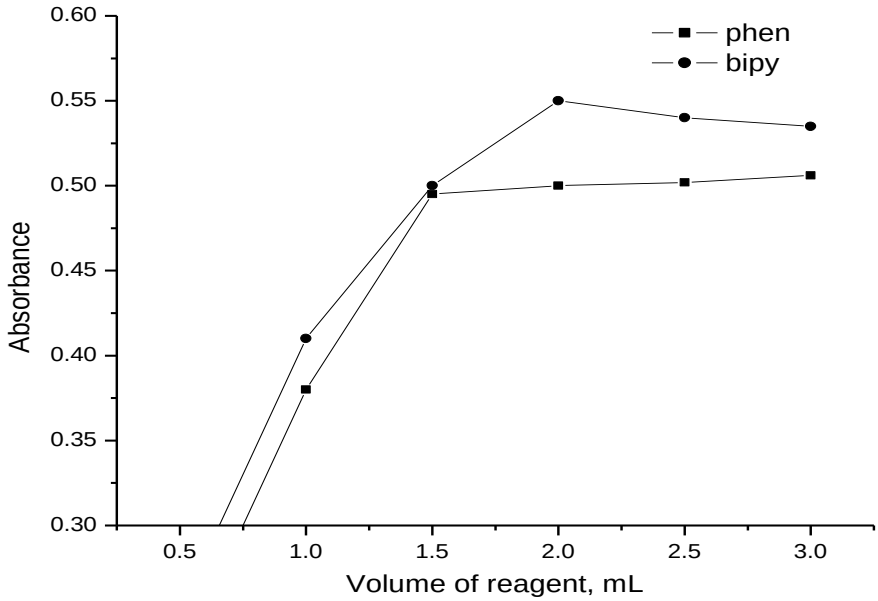

Figure 3: Effect of 1, 10-phenanthroline (4 µg mL^{-1} KTF) and 2, 2´-bipyridyl (15 µg mL^{-1} KTF)

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B. Method Validation

Linearity, sensitivity, limits of detection and quantification

The linearity obtained in the calibration graph from 0.4–8.0 µg mL^{-1} and 0.4-10.0 µg mL^{-1} KTF in Method A and Method B, respectively proves the validation for linearity, selectivity, precision, accuracy, robustness and ruggedness and recovery. Following equation is used for calibration graph

Y = a + bX,

b=slope

a = intercept

(where, Y = absorbance, X = concentration in µg mL^{-1}). Molar absorptivity and Sandell sensitivity values and the limits of detection and quantification were obtained from ICH guidelines [34] by the formulae: LOD = 3.3 S/slope and LOQ = 10 S/slope,

where, S = standard deviation for absorbance of seven blank readings. Table .1.

C. Intra-day and Inter-day Precision and Accuracy

To value the precision and accuracy the study was repeated by intra-day precision and inter-day precision. Three levels of analyte was chosen for each method. Table 2.

%RSD values were ≤ 3.31% (intra-day) and ≤ 3.56% (inter-day) which indicates good precision of the methods. %RE was ≤ 3.55% demonstrating the high accuracy of the proposed methods.

Table 1: Sensitivity and Regression Parameters

Parameter	Method A	Method B
λ_{max}, nm	510	520
Linear range, µg ml^{-1}	0.4-8.0	1.0-25.0
Molar absorptivity(ε), l mol^{-1} cm^{-1}	5.40×10^4	1.6×10^4
Sandell sensitivity*, µg cm^{-2}	0.0079	0.0254
Limit of detection (LOD), µg ml^{-1}	0.15	0.27
Limit of quantification (LOQ), µg ml^{-1}	0.46	0.80
Regression equation, Y**		
Intercept (a)	0.0061	0.0024
Slope (b)	0.1227	0.0392
Standard deviation of a (S_a)	0.0674	0.0130
Standard deviation of b (S_b)	0.0150	0.0010
Regression coefficient (r)	0.9997	0.999

*Limit of determination as the weight in µg per ml of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and l = 1 cm. **Y=a+bX, Where Y is the absorbance, X is concentration in µg ml^{-1}, a is intercept, b is slope.

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Table 2: Evaltion of Intra-day Accuracy and Inter-day and Precision

Methods*	KTF taken µg ml^{-1}	Intra-day accuracy and precision (n = 7)			Inter-day accuracy and precision (n = 5)		
		KTF found µg ml^{-1}	%RE	%RSD	KTF found µg ml^{-1}	%RE	%RS
Method A	2.0	2.03	1.60	1.92	2.04	2.36	1.9
	4.0	3.95	1.02	0.90	3.94	1.35	0.8
	6.0	6.04	0.75	1.29	6.06	1.06	1.3
Method B	10.0	9.92	0.74	0.62	9.92	0.74	0.6
	15.0	15.15	1.10	1.02	15.20	1.40	1.0
	20.0	20.29	1.50	0.45	20.35	1.80	0.4

RE. Relative error; RSD. Relative standard deviation.

D. Robustness and Ruggedness

With incremental changes in $FeCl_3$ and Phen/Bipy concentrations (n = 3) and conducting the experiments using 2, 4 and 6 µg mL^{-1} (Method A) and 10, 15 and 10 µg mL^{-1}KTF (Method B) robustness was tested. With the altered $FeCl_3$ and Phen/Bipy concentrations RSD were < 1.5%. Further, a drug solution at different concentration levels were analyzed by four different chemist, and with three different cuvettes by a single chemist. RSD were <1% for inter-analysts, whereas RSD were < 2% for the inter-instrumental variation. (Table 3).

Table 3: Robustness and Ruggedness Expressed as Intermediate Precision (%RSD)

Methods	KTF Taken (µg ml^{-1})	Method robustness		Method ruggedness	
		Parameter altered			
		Ferric chloride (0.0033 M)* ml %RSD (n = 3)	Reaction time** %RSD (n=3)	Inter-analysts' %RSD (n = 4)	Inter-instruments' %RSD (n = 3)
Method A	2.0	0.94	1.02	0.71	1.23
	4.0	1.05	0.98	0.94	1.49
	6.0	0.89	1.09	0.87	1.37
Method B	10.0	1.12	1.05	1.07	1.21
	15.0	1.01	1.16	0.95	1.37
	20.0	1.17	1.19	1.01	1.29

*Ferric chloride volumes used were 1.8, 2.0 and 2.2 ml in **reaction time of 8, 10 and 12 min in method A

D. Application to tablets

For quantification of KTF in commercial tablets a potentiometric titration using 0.1 M perchloric acid as titrant was conducted. The results obtained by the proposed methods was in agreement with reference method. The results of assay are tabulated in Table 4.

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Table 4: Results of Analysis of Tablets by the Proposed Methods and Comparison with the Official Method

Tablets analysed	Label claim, mg/tablet	Found* (Percent of label claim ± SD)		
		Reference method	Proposed methods	
			Method A	Method B
[a]Asthafen	1	100.8 ± 0.91	100.6 ±0.86 t= 1.22 F= 1.11	101.2 ± 0.75 t= 1.55 F= 1.47
[b]Ketasma	1	102.3 ± 1.02	101.3 ± 1.06 t= 2.26 F= 1.07	101.5 ± 0.88 t= 0.97 F= 1.34

*Mean value of five determinations;
[a]Torrent pharmaceuticals, Sikkim, India,[b] Sun pharmaceuticals, Sikkim, India.
Tabulated t-value at the 95% confidence level is 2.78; Tabulated F-value at the 95% confidence level is 6.39.

E. Recovery Study (Standard Addition Method)

Standard-addition technique was applied for recovery experiments to assess the accuracy. The recovery was measured by determining the agreement between the measured standard concentration and added known concentration to the sample. By spiking the pre-analyzed tablet KTF with pure KTF at different levels and the total was found by the above methods. Where, the recovery percentage values ranged between 96.4 and 101.5% with standard deviation in the range 1.58-2.63%. Closeness of the results to 100% showed the good accuracy of the methods. The results are tabulated in Table 5

Table 5: Results of Recovery Study via Strandard Addition Method

Method	Tablet studied	KTF in tablet $\mu g\ mL^{-1}$	Pure KTF added $\mu g\ mL^{-1}$	Total found $\mu g\ mL^{-1}$	Pure KTF * Percent ± SD
A	Ketasma-1	3.04	1.5	4.54	100.5 ± 1.98
		3.04	3.0	6.07	101.3 ±1.05
		3.04	4.5	7.63	102.0 ± 1.71
B	Ketasma-1	7.60	3.75	11.42	100.5 ± 1.26
		7.60	7.50	15.39	102.1 ± 1.98
		7.60	11.25	19.15	101.6 ± 1.34

* Mean value of three determinations

V. CONCLUSION

This paper presents two spectrophotometric methods for the assay of ketotifen fumarate in tablets and bulk and validated according to current ICH guidelines. Present methods are advantageous over the formerly reported spectrophotometric methods. The methods involve neither heating nor extraction. The procedure makes use of cheaper and readily available chemicals and redox and complex formation reactions. Interference produced from common tablet excipients is completely nil here because the absorbance is measured at longer wavelength. Hence, above said procedures are appropriate for the assay and evaluation of drugs in pharmaceutical industrial quality control.

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Received: 16 Apr 2020 | Revised: 22 Apr 2020 | Accepted: 12 May 2020

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DOI: 10.37200/IJPR/V24I5/PR2020680
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DOI: 10.37200/IJPR/V24I5/PR2020680
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