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Visible Spectrophotometric Method for Determination of Naftopidil and Telmisartan in Bulk and Pharmaceutical Formulations by Tropaeoline-ooo

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ABSTRACT

A simple and sensitive Spectrophotometric method for the determination of Naftopidil and Telmisartan in bulk and in pharmaceutical formulations has been developed and validated. This method is based on extraction of these drugs into chloroform as ion-pair with azo dyes such as Tropaeoline-ooo (TPOOO). The optimum conditions of the reactions for the proposed method were studied and optimized. Results of the assay were statistically validated and recorded. The proposed method was applied successfully for the determination of Naftopidil and Telmisartan in commercial tablet dosage form and no significant interference was observed from the excipients commonly used as pharmaceutical aids with the assay procedure. System suitability, specificity, linearity, accuracy and precision were performed.

Keywords: Naftopidil, Telmisartan, Tropaeoline-ooo (TPOOO), Chloroform, Visible Spectrophotometer.

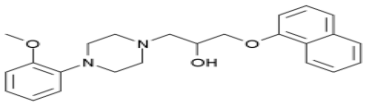
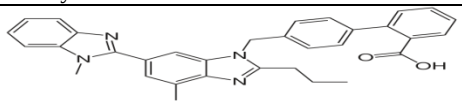
INTRODUCTION

Naftopidil is a phenyl piperazine derivative and alpha 1-adrenoceptor antagonist. It is used for the bladder outlet obstruction in patients with benign prostatic hyperplasia (BPH) and utilized extensively for the treatment of arterial hypertension [1-6]. Naftopidil has distinct characteristics because it has a three times greater affinity for the α1D-adrenergic receptor subtype than for the α1A subtype. Naftopidil is strongly suppressed cell proliferation of stromalcells, resulting in decreased tumorigenic soluble factor, suggesting that Naftopidil might be effective in preventing stromal support of tumor cells.

Telmisartan is a potent, long lasting, orally acting nonpeptide antagonist of angiotensin II Type 1receptor (AT1) used in the management of hypertension. It selectively inhibits stimulation of the AT1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation [7]. Several studies recently [8] suggest that the effects of Telmisartan are mediated via not only blockade of ARB but also activation of peroxisome proliferators-activated- γ receptor (PPAR -γ) a central regulator of insulin and glucose metabolism. It is believed that Telmisartan dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD). The coexistence of hypertension and diabetes increases the risk for macrovascular and microvascular complications, thus predisposing patients to cardiac death, congestive heart failure, coronary heart disease,

cerebral and peripheral vascular diseases, nephropathy, and retinopathy [9]. Antihypertensive treatment in diabetics decreases cardiovascular mortality and slows the decline in glomerular function.

Drug Profile:

Name	Naftopidil	Telmisartan
Chemical name (Systematic IUPAC name)	1-[4-(2-methoxyphenyl) piperazin-1-yl]-3-(1-naphthyloxy) propan-2-ol	4[(1, 4-dimethyl-2-propyl (2, 6-bi-1H-benzimidazol]-1-yl) methyl] [1, 1-biphenyl]-2-carboxylic acid.
Structure		
Molecular formula	$C_{24}H_{28}N_2O_3$	$C_{33}H_{30}N4O2$
Empirical formula	$C_{24}H_{28}N_2O_3 \cdot xHCl \cdot yH_2O$	$C_{33}H_{30}N4O2$
Molecular weight	392.49 g/mol	514.617 g/mol
Color	Solid-white	Solid-white
pKb	7.32	pKa 3.65 (strong acidic) pKa 6.13 (strong basic)
Melting Point	125-126^{0}c	261-263^{0}c
Solubility	Acetonitril:0.1M HCl (25:75v/V), Insoluble in water	Insoluble in water (0.0035 mg/ml) alkalised soluble, At low P^H media (HCl),& DMF
Pharmacodynamic/ chem. category	Anti-hypertension drug	Anti-hypertension drug

Literature Survey on the analytical methods for Naftopidil and Telmisartan: Literature survey reveals that the Naftopidil and Telmisartan has some published methods for estimation of assay and impurity profile by HPLC and UV/visible spectroscopy techniques [10-22].Analytical methods for the quantitative determination of Telmisartan in pharmaceutical formulations are described in literature like titrimetric [23], voltametry [24], Spectroflourimetric [25], UV spectrophotometric [26] methods in human plasma have been reported. The objective of the research is to develop a simple visible method. Method validation has performed as per the ICH and regulatory guidelines and review articles were revealed for method development and validation.

MATERIALS AND METHODS

Instrument and chemicals: A Systronics-119 UV-Visible spectrophotometer with pc connection was used for spectral and absorbance measurements. Sartorius BT 224s analytical balance was used for this research experiments. The reference samples of Naftopidil and Telmisartan were supplied as a gift sample from Hetero labs limited, Hyderabad. The commercially available Naftopidil, Telmisartan solid dosage forms were procured from the local market. All the chemicals used were of analytical grade and the solutions were prepared with double distilled water.

Preparation of standard drug solution (1mg mL^{-1})

Naftopidil: The stock solution (1mg/ml) was prepared by dissolving 100 mg of it in 100mL of 25:75 (v/V) of acetonitrile: 0.1M HCl. A portion of this stock solution was diluted with the diluent to obtain the working standard drug solution of concentrations of 100µg mL^{-1}.

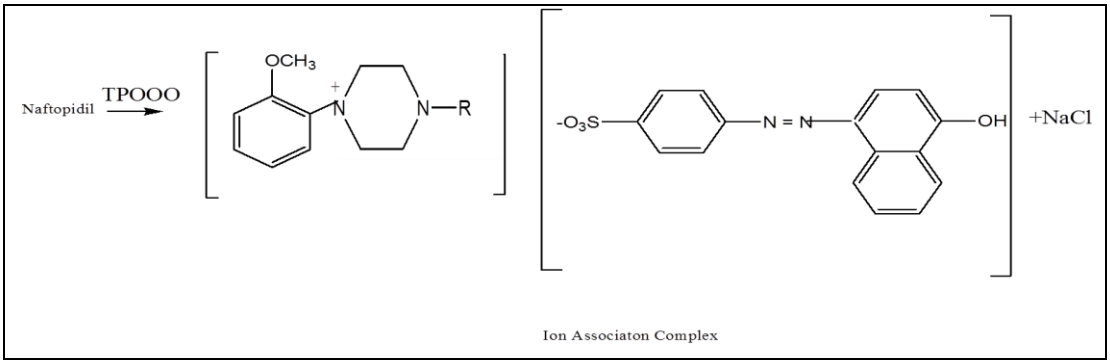
Telmisartan: 100mg of drug was accurately weighed and transferred to separate 100mL volumetric flask. To dissolve the drug 10mL of 0.05M HCl solution was added to flask and the volume was making up to the mark with0.05M HCl solution.

Preparation of reagents:

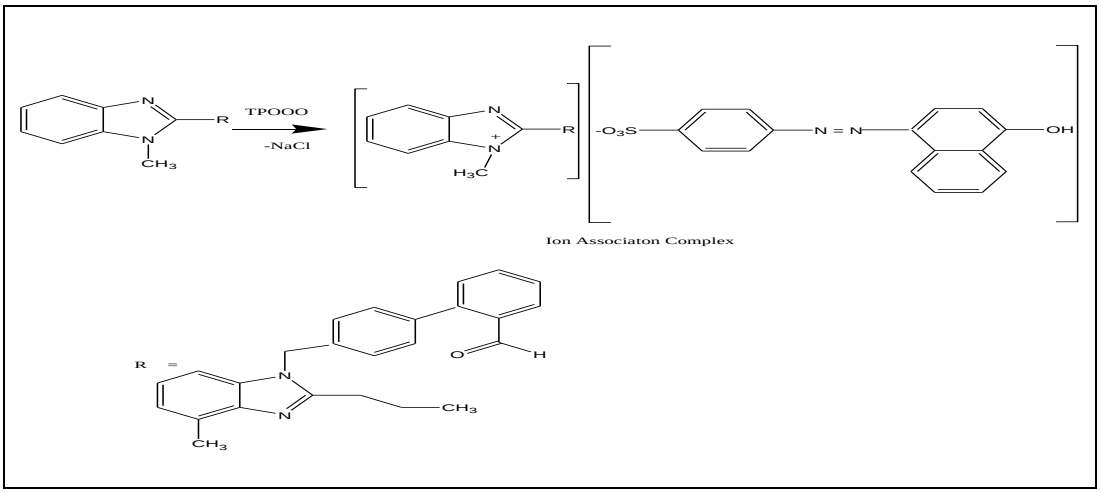
TPOOO Solution Loba, 0.2%	Prepared by dissolving 200mg of TPOOO in 100ml of double distilled water.
HCl solution Qualigens, 0.1M	Prepared by diluting 8.6 ml of Con.HCl to 1000ml of distilled water and standardized.
Chloroform	AR grade chloroform was used as it is.

Scheme: The Naftopidil and Telmisartan form an ion association complex (Orange color) with TPOOO which is extractable into chloroform from aqueous phase. The protonated nitrogen (positive charge) of Naftopidil and Telmisartan were expected to attract the oppositely charged part of the dye and behave as single unit being held together by electro static attraction. The reaction pathway can be represented in scheme I & II. Possible reaction mechanism of Naftopidil and Telmisartan with TPOOO /HCl is

Scheme- I:



Scheme-II:



General procedure: Aliquots of standard Naftopidil solution (0.1-0.6mL), 0.004 – 0.024 mg mL^{-1}, were placed in a series of 125 mL separating funnels. A volume of 5.0 mL of 0.1M HCl, and 2.0 mL of TPOOO were added successively. The total volume of aqueous phase in each separating funnel was adjusted to 15 mL with distilled water. Then 10 mL of chloroform was added to each separating funnel and the contents were shaken for 2 min. and allowed to separate. The organic layer was collected through cotton plug and the absorbance was measured immediately at 502 nm against a reagent blank. The colored species was stable for 1 hour. The amount of Naftopidil in the sample solution was obtained from the Beer's law plot.
Aliquots of standard Telmisartan solution (0.1-0.6mlor 10-60 µg mL^{-1}) were placed in a series of 125 mL separating funnels. A volume of 5.0mL of 0.1M HCl and 1.5mL of TPOOO were added successively. The

total volume of aqueous phase in each separating funnelwas adjusted to 15 mL with distilled water. Then 10 mL of chloroform was added to each separating funnel and the contents were shaken for 2 min. and allowed to separate. The organic layer was collected through cotton plug and the absorbance was measured immediately at 500 nm against a reagent blank. The colored species was stable for 1 h. The amount of Telmisartan in the sample solution was obtained from the Beer's law plot.

RESULTS AND DISCUSSION

Naftopidil contain active functional moieties such as tertiary amine, phenyl piperazine ring, secondary alcohol, and oxidizing centers.Telmisartan possesses different functional moieties such as tertiary amine, benzimidazole, imidazole and oxidizing centers.

An attempt has been made to indicate the nature of colored species formed in the proposed method for the determination of Naftopidil and Telmisartan based on analogy. The selectivity of the reaction may increase by appropriate organic solvent as an extractant which then depends upon parameters such as polarities of the amine and of the dye.

Optimization of the conditions on absorption spectrum of the reaction product: The condition under which the reaction of Naftopidil and Telmisartan with Tpooo and HCl fulfills the essential requirements was investigated. All conditions studied were optimized at room temperature (31 $\pm 2^0$C).

Selection of reaction medium: To find a suitable media for the reaction, different acidic mediums have been used. The best results were obtained when 25:75 (v/V) of acetonitrile: 0.1M HCl for Naftopidil and 0.05M HCl for Telmisartan were used to a constant concentration and the results were observed. From the absorption spectrum it was evident that the solutions were found optimum. Larger volumes had no significant effect on the absorbance of the colored species.

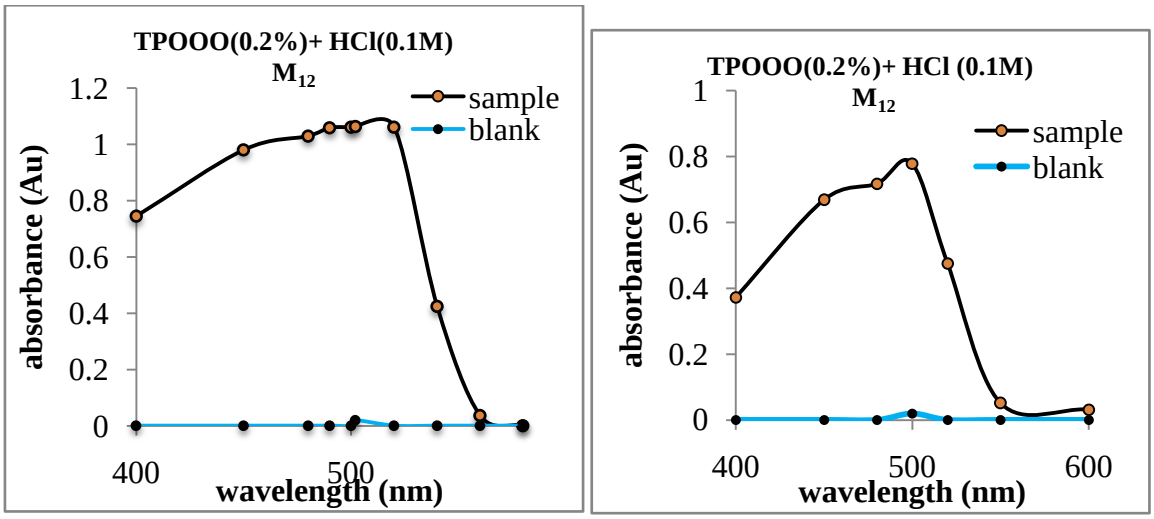
Effect of order of addition of reactants: The orders of addition of reactants are Drug + HCl + TPOOO

Effect of TPOOO concentration: Several experiments were carried out to study the influence of TPOOO concentration on the color development by keeping the concentration of drug and HCl to constant and changing reagent concentration (0.5 – 3.0mL). It was apparent that 2 ml of TPOOO for Naftopidil and 1.5 mL of TPOOO for Telmisartan gave maximum color.

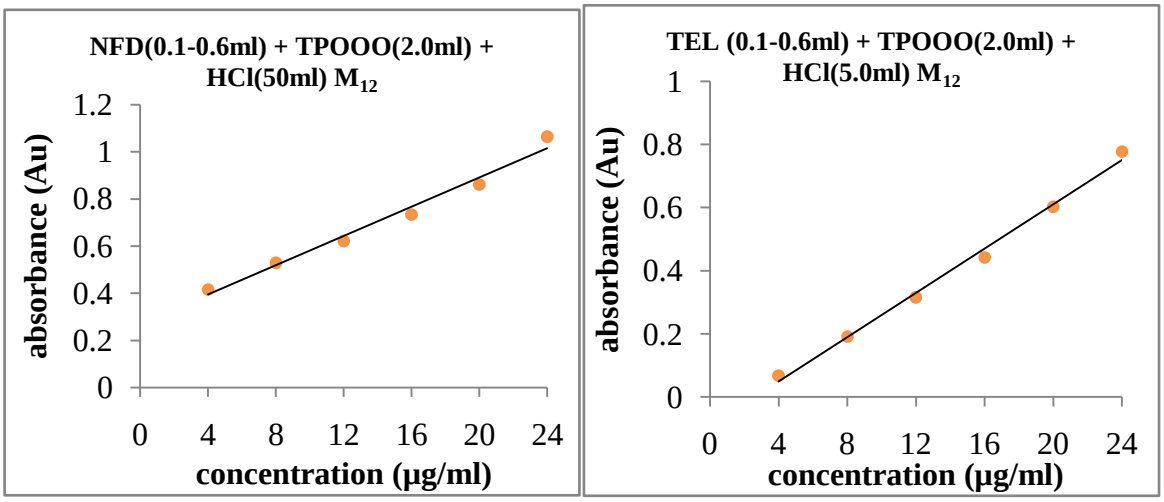
Effect of HCl concentration: Several experiments were carried out to study the influence of HCl concentration on the color development by keeping the concentration of drugs, TPOOO to constant and changing HCl concentration. It was apparent that 5 mL of reagent gave maximum color.

Reaction time and stability of the colored species: The color reaction was not instantaneous. Maximum color was developed within 5 min of mixing the reactants and was stable for 2 h thereafter.

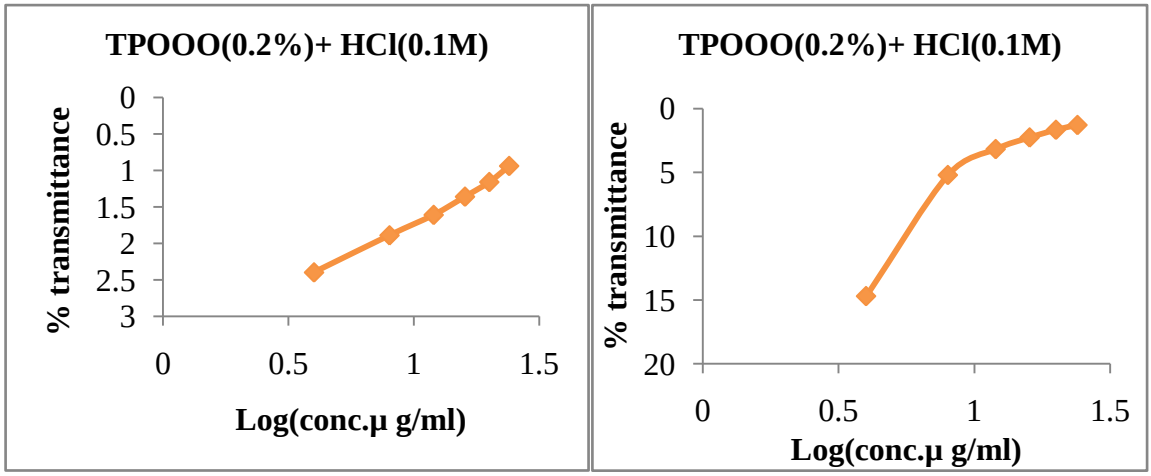
Absorption spectrum and calibration graph: Absorption spectrum of the colored complex was scanned at 400-600 nm against a reagent blank. The reaction product showed absorption maximum at 502 nm for Naftopidil and 500 nm for Telmisartan. Calibration graph was obtained according to the above general procedure and the graphs are shown in figures 1-6.



Figs 1, 2: Absorption spectra of Naftopidil and Telmisartan with TPOOO



Figs: 3, 4: Beer's law plots of Naftopidil and Telmisartan



Figs 5, 6: Ringbom plot of Naftopidil and Telmisartan-TPOOO

The linearity replicates for six different concentration of Naftopidil and Telmisartan was checked by a linear least - squares treatment. All the spectral characteristics and the measured or calculated factors and parameters were summarized in table 1.

Table: 1 Optical and regression characteristics of the proposed methods

Parameter	Naftopidil	Telmisartan
λ max (nm)	502	500
Beer's law limit (µg/ml)	4-24	4-24
molar absorptivity,L/mol.cm	$1.7953x10^{-2}$	$7.763x10^{-3}$
sandell's sensitivity (µg/cm^2/0.001 absorbance unit)	$1.4x10^{-5}$	$1.4x10^{-5}$
Slope(b)	1.2422	1.402
Intercept(a)	0.2698	-0.0912
Correlation coefficient ®	0.9902	0.9968
r^2	0.9806	0.9937
Average	0.7046	0.3995
Sd	0.2346	0.2631
Standard error on estimation(s_e)	0.1071	0.1201
Standard deviation on slope (s_b)	0.256	0.2871
Standard deviation on intercept (s_a)	0.0997	0.1118
LOD	0.2649	0.2632
LOQ	0.8027	0.7975
% RSD	0.2326	0.4402
Precision: 0.01level	0.1148	0.1010
Precision: 0.05 level	0.0799	0.0703

Specificity: Results of tablet solutions showed that there is no interference of the excipients when compared with the working standard solution. Thus, the method was said to be specific.

Accuracy: For the accuracy of proposed methods, recovery studies were performed by standard method at three different levels (50%, 75 % and 125% of final concentration). A known amount of standard pure drug was analyzed by proposed methods. Results of recovery studies were found to be satisfactory.

Precision: The Repeatability of the proposed methods was ascertained by three replicates of fixed concentration (0.6 mg mL^{-1}) within the Beer's range and finding out the absorbance by the proposed methods. The method precision was carried out by intraday and interday measurement. From this absorbance % RSD was calculated. The calculated % RSD observed is well below 0.2326% for Naftopidil and 0.44% for Telmisartan indicates that the methods are precise.

APPLICATIONS

The method proposed in this work is based on the reactivity of Naftopidil and Telmisartan with Tropaeoline-ooo and was used to produce color species with reasonable stability paving possibility for the determination of the drugs in bulk and pharmaceutical formulations by visible spectrophotometry. The results are presented in table 2.

Table-2: Assay and recovery studies of proposed methods for drugs in Pharmaceutical formulations

Naftopidil				Telmisartan			
Formulation Tablet	Labeled amount	Avg±std.dev	% recovery	Formulation Tablet	Labeled amount	Avg±std.dev	% recovery
Naftomax Nafodil	50 mg	49.867±0.0665 T = 1.12 F =0.67	99.39%	Cresar Hytel	80 mg	79.865±0.10254 T = 0.47 F =0.56	99.57%
Nafodil Naftomax	75 mg	74.843±0.1176 T = 0.32 F =0.54	99.63%	Arbitel Adcom	40 mg	39.836±0.1146 T = 0.35 F =1.07	99.93%

CONCLUSIONS

Naftopidil and Telmisartan were estimated successfully by the developed extractive spectrophotometric methods, a pure compound and as a pharmaceutical formulation. The proposed methods were suitable and valid for application in laboratories lacking of liquid chromatographic or other sophisticated instruments. These methods were simple, rapid, accurate, and does not involve any critical reaction conditions, or tedious sample preparation. It is unaffected by slight variations in experimental conditions such as pH, dye concentration, shaking time and temperature. Hence, these proposed methods can be used for the routine analysis of the cited drugs in their available dosage forms.

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