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Spectrophotometric determination of ion-pair complexes of alverine citrate and tapentadol using bromophenol blue

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ABSTRACT

The objective of the present work is to develop simple, precise and accurate colorimetric methods for the estimation of alverine citrate (ALV), tapentadol (TAP) using bromophenol blue (BPB) reagent. The method was developed on Perkin Elmer LAMBDA 25 UV –VIS spectrophotometer with 1cm quartz cells. The methods are based mainly on the formation of ion-pair complexes of the drugs with acidic dye; bromophenol blue followed by extraction into organic solvent. The colored complexes exhibited maximum absorbance measured at 423 nm for ALV, 416 nm for TAP, respectively. The linearity was assessed and found to be 20-100 µg/ml for ALV, 100-500 µg/ml for TAP, respectively. The colorimetric methods were extensively validated as per ICH guidelines and all the parameters were within the acceptance criteria with correlation of 0.9999. The accuracy and precision studies showed % RSD less than 2 for both the methods. The methods were proved to be more accurate, simple, precise and rapid by statistical validation, hence could be applied for regular analysis.

Key words: Alverine citrate(ALV), Tapentadol(TAP), Bromophenol blue(BPB), Chargr transfer(CT)

INTRODUCTION

Alverine (Fig-1) chemically is citrate form of *N*-Ethyl-3-phenyl-*N*-(3-phenylpropyl)propane-1-amine a smooth muscle relaxant used for functional gastrointestinal disorders. Alverine acts directly on the smooth muscle, causing it to relax. This prevents the muscle spasms which occur in the gut in conditions such as irritable bowel syndrome and diverticular disease. Tapentadol chemically is 3-[(1R,2R)-3-(dimethyl amino)-1-ethyl-2-methylpropyl] phenol is a centrally acting analgesic with a dual mode of action as an agonist of the µ-opioid receptor and as a norepinephrine reuptake inhibitor.

Literature survey of these drugs revealed that there are very few methods for the determination of, TAP(1-6) and ALV(7-10) by chromatographic and spectrophotometric methods. The reported methods suffer from one or more disadvantages such as narrow linear response, lack of sensitivity and selectivity and usage of expensive reagents. The need for sensitive, cost effective and reliable spectrophotometric methods for the selected drugs is thus obviously recognised. Spectrophotometry is by far the instrumental technique of choice in the laboratories of under developed and developing nations for the quantification of drugs owing mainly to its simplicity, high sensitivity and selectivity and often demanding low cost equipment. The π-acceptors have been extensively used in the spectrophotometric analysis of various drugs which could act as electron donors. CT bands are easily identified because they are very intense, i.e. have a large extinction coefficient, are normally broad and display very strong absorptions that go above the absorption scale (dilute solutions must be used). The appearance of the CT band is attributed to the excitation of an electron from the highest occupied molecular orbital of the donor to the lowest unoccupied molecular orbital of the acceptor. The position and intensity of the CT bands are useful for identification and analysis of the nature of donors and acceptors qualitatively and quantitatively. The present colorimetric methods were proposed in view of the need for simple, rapid, economic methods for the estimation of both drugs.

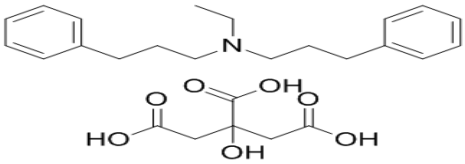

Fig: 1 Structure of ALV

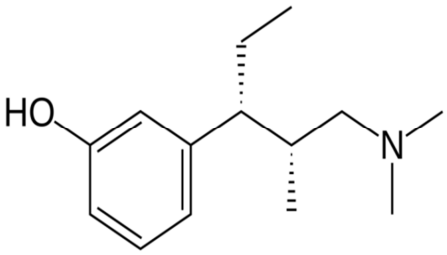

Fig: 2 Structure of TAP

MATERIALS AND METHODS

Instrumentation
Double-beam Perkin Elmer (LAMBDA 25) UV-Vis spectrophotometer was used for spectral measurements.

Chemicals and reagents
ARP and TAP are obtained as gift samples from Aurobindo Pharma Ltd, Hyd., chloroform and bromophenol blue of AR Grade were used for the experimental work.

Preparation of samples
Preparation of stock solution for estimation of ALV
Accurately weighed 25 mg of ALV was transferred to a 50 ml volumetric flask, dissolved and diluted to final volume with water. The resulting solution has a concentration of 0.5 mg/ml. Standard solutions were further prepared using stock solution.

Preparation of stock solution for estimation of TAP
Accurately weighed 25 mg of TAP was transferred to a 25 ml volumetric flask, dissolved and diluted to final volume with water. The resulting solution has a concentration of 1 mg/ml. Standard solutions were further prepared using stock solution.

Preparation of calibration standards for ALV and TAP
As per the linearity range given in the table, all the calibration standards were prepared using the specified diluent and followed as per order of reagent addition given in the table 1. The absorbances were measured at the λ_{max} of the reaction product given in the table 3.

Assay procedure for ALV
Twenty tablets of commercial samples (Spasverin 60 mg) of ALV were accurately weighed and powdered. Tablet powder equivalent to 25 mg was weighed and dissolved in 50 ml water filtered and the procedure was carried out as mentioned above.

Assay procedure for TAP
Twenty tablets of commercial samples of TAP (Tapenta 100 mg) were accurately weighed and powdered. Tablet powder equivalent to 25 mg was weighed and dissolved in 25 ml water, filtered and the procedure was carried out as mentioned above.

RESULTS AND DISCUSSION

Optimisation of the Method
The spectral characteristics of all the methods using bromophenol blue reagent was performed by optimizing the methods for several optimization parameters as given below. Figure3 and 4 represents the absorption spectrum of ALV and TAP and figure 5 represents the overlay spectra, respectively.

Order of addition
To find out whether the order of addition of reagents has any influence, the absorbance of a set of solutions prepared by mixing in different sequences, fixed amount of drug and reagent as given in recommended procedure were measured. The best order was reagent followed by drugs and chloroform.

Table 1 Order of addition and concentration of reagents

0.25 ml BPB (0.1%w/v) + TAP + 0.1 ml Ortho phosphoric acid (0.1%v/v) + chloroform
0.7 ml BPB (0.1%w/v) + ALV + 0.1 ml Ortho phosphoric acid (0.1%v/v) + chloroform

Reagent concentration

In order to obtain the optimum conditions for determination of drugs, the absorbances were measured for a series of solutions by varying the concentration of one with respect to other against the corresponding reagent blank in each case. The optimum conditions were presented in table 1.

Effect of temperature and time

Effect of temperature on reaction conditions was studied by lowering/increasing the temperature for the reaction products. At very low temperatures the intensity of the colour formed is very low and at high temperatures the colour is not stable as the intensity of it decreases. Variation in the time interval also causing an effect on the absorbance of drug as shown, at a minimum time interval of 5-10 min the absorbance of the drug increased and at above 15min the absorbance values remained stable and after a period of 1 hour time interval the colour intensity decreased which was known from the absorbance values obtained. Figure 3 shows the effect of temperature and time on the drugs using bromophenol blue reagent.

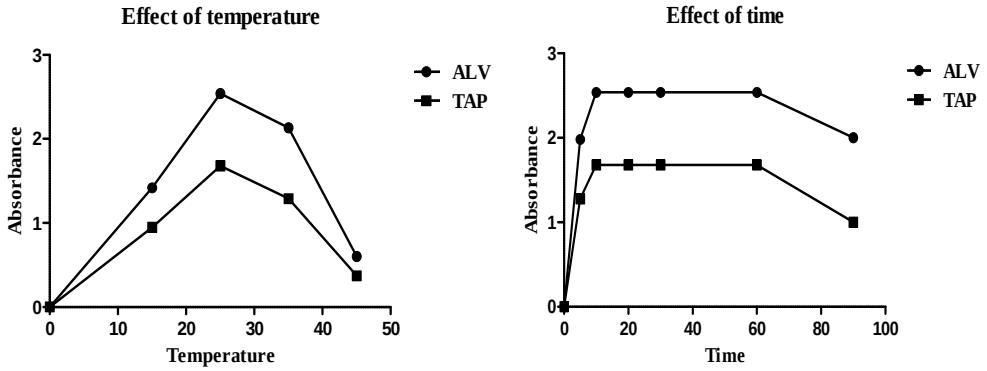

Fig: 3 Effect of temperature and time on ALV and TAP using bromophenol blue

Stability of colour

The influence of the time on the maximum colour development and stability of the coloured species were studied by measuring the absorbance's at gradual increase in time interval.

Effect of solvent

The solvent used is chloroform in which the drugs are completely soluble and the intensity of the colour, stability of the drug was found to be good. When tested with certain solvents like DMF, DMSO, ethanol the results seen were not satisfactory as the development of the colour and the stability was not found. So finally chloroform was selected by which the results obtained were found to be satisfactory.

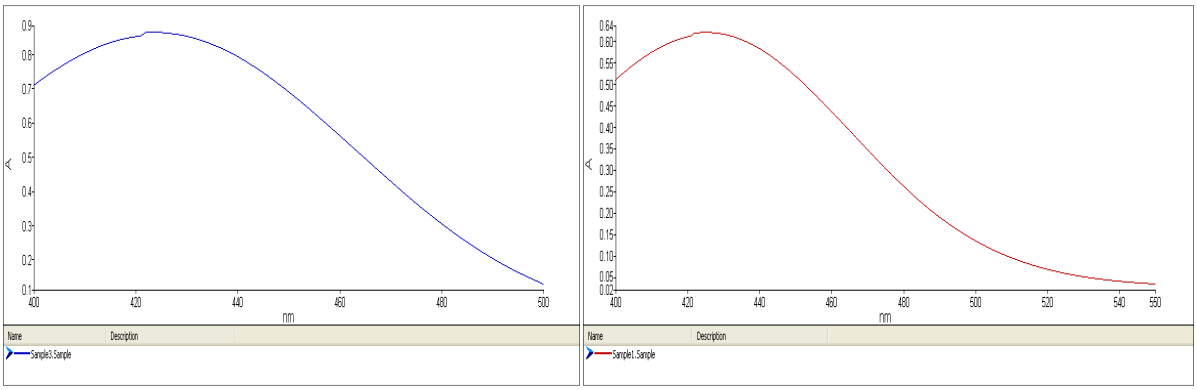

Fig:4 Absorption spectrum of ALV Fig:5 Absorption spectrum of TAP

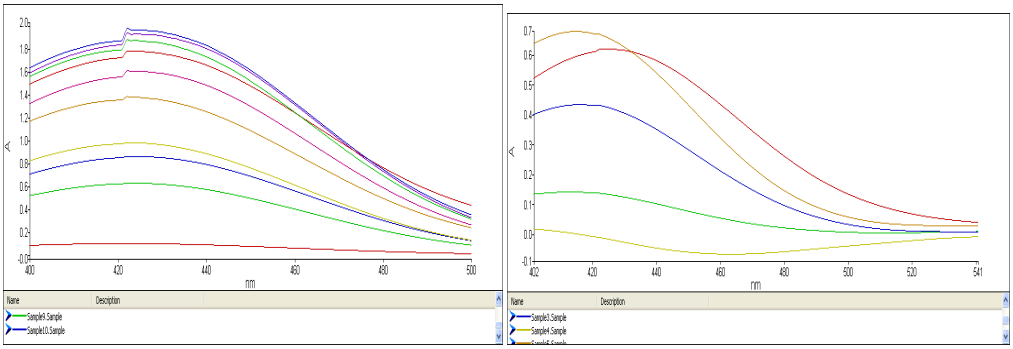

Fig: 6 Overlay spectra of alverine citrate and tapentadol with BPB

Method validation

All the methods were validated for accuracy, precision, linearity, LOD, LOQ, ruggedness and robustness and other validation parameters.

Linearity and range

At the described experimental conditions for ALV/TAP standard calibration curves were constructed by plotting an increase in absorbance with concentration as shown in fig 7and 8. A linear correlation was found between absorbance and concentration of ALV/TAP as given in table 2 and all the results regarding linearity were given in table 3. The statistical parameters given in the regression equation were calculated from the calibration graphs. The high values of the regression coefficients and low values of y-intercepts of the regression equations, proved the linearity of the calibration curves.

Table 2 Table showing linearity for ALV and TAP

ALV		TAP	
Conc (µg/ml)	**Absorbance**	**Conc (µg/ml)**	**Absorbance**
20	0.541	100	0.10
40	1.08	200	0.195
60	1.60	300	0.288
80	2.13	400	0.384
100	2.64	500	0.485

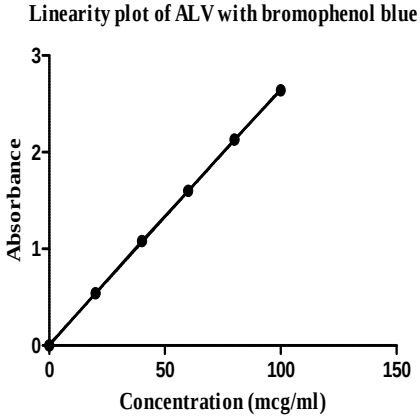

Fig:7 linearity plot of ALV

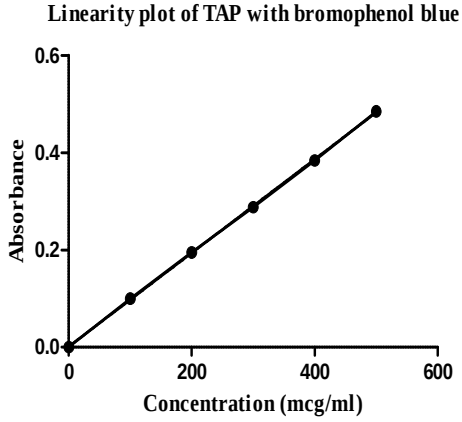

Fig:8 linearity plot of TAP

Table 3 Optical and regression parameters for ALV and TAP

Parameters	ALV	TAP
λ_{max} nm	423	416
Beer's law range (µg/ml)	20-100	100-500
Molar extinction coefficient (lit. mol^{-1} cm^{-1})	2.6×10^{6}	9.6×10^{4}
Sandell'ssensitivity (µg/cm^2)/0.001 absorbance unit	6×10^{4}	3×10^{5}
LOD, µg/ml	1.37	8.49
LOQ, µg/ml	4.16	25.73
Slope(m)	0.02641	0.0009629
Intercept(b)	0.01133	0.001286
Correlation coefficient(r)	0.9999	0.9998

Precision

The precision of the proposed methods were assessed by determining the relative standard deviation (RSD) of six replicate analyses on the same solution containing fixed concentration of ALV/TAP (within Beer's law limit). The low % RSD of the intraday and interday repeatability studies corroborates precision of the method. Table 4 represents the results of precision studies.

Table 4 Results of precision studies

Parameter	ALV		TAP	
	Intra day*	Inter day*	Intra day*	Inter day*
Conc, µg/ml)	60		300	
Mean abs	1.606	1.608	0.283	0.283
SD	0.008164	0.009832	0.003312	0.004037
% RSD	0.51	0.614	1.17	1.422

**Mean of six determinations*

Robustness

Robustness was checked by narrow alteration of the optimized parameters and the % RSD were found to be satisfactory.

Ruggedness

System to system/ analyst to analyst/ variability study was conducted on different colorimeters and the results were satisfactory and reported in table 3.

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

LOD and LOQ were determined by analysing progressively lower concentrations of standard solution using optimized conditions and the results were found to be satisfactory and were presented in table 3.

Accuracy

The validity and accuracy of the proposed methods were further assessed by recovery studies using the standard addition technique. For this purpose, a known amount of pure drug at three different levels was spiked to the fixed and known quantity of pre analysed formulation samples and the nominal value of drug was estimated by the proposed methods. The results given in table 5 establish that the methods were reproducible by low SD and %RSD. No interference was evidenced from the commonly encountered formulation excipients.

Table 5 Accuracy table for the methods

Drug	Drug in formulation (µg)	Std added (µg)	Amt Found (µg)	%Recovered	%RSD N=3
ALV	60	20	79.22	99.02	0.790
	60	60	119.33	99.44	0.473
	60	100	159.30	99.56	0.588
TAP	300	100	399.42	99.85	0.158
	300	300	598.87	99.81	0.095
	300	500	799.65	99.95	0.026

Application of the proposed methods to formulations

To evaluate the proposed methods, they were applied to the determination of ALV/TAP in commercial formulations. The recoveries are close to 100%, indicating that there is no serious interference in samples. The good agreement between these results and known values indicate the successful applicability of the proposed methods for the determination of ALV/TAP in formulations. The results are given in table 6.

Table 6 Assay results for methods

Formulations	Label claim (mg)	Amount found(mg)	%Recovery N=3
Spasverin(tablet)	60	59.75	99.58
Tapenta (tablet)	100	99.75	99.75

CONCLUSION

Two new, cost effective, simple and sensitive visible spectrophotometric methods, using bromophenol blue as reagent, were developed for the determination of ALV and TAP in bulk and in pharmaceutical formulations. The developed methods were also validated. From the statistical data, it was found that the proposed methods were

accurate, precise and reproducible and can be successfully applied to the analysis of the same and could make a better alternative to the existing methods.

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