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Determination of Bazedoxifene Acetate in Bulk with the Aid of Uv-Spectroscopy: Development and Validation

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Abstract: A simple, rapid, accurate, and economical UV-spectrophotometric method has been developed for the estimation of bazedoxifene acetate from bulk. The developed method is validated as per ICH guidelines. The method uses a shimadzu UV-Visible spectrophotometer (model no.8400S) with matched quartz cells (1 cm) for the estimation of drug from bulk. The λ_{max} of bazedoxifene acetate in methanol was found to be 298 nm and in simulated gastric fluid (SGF) 299nm. The drug follows linearity in the concentration range 2–10 µg/mL with a correlation coefficient value of 0.999 and 0.998 respectively. The accuracy of the method was checked by recovery experiment performed at three different levels, i.e., 80%, 100%, and 120%. The % recovery was found to be in the range of 97– 99.83%. The low values of % RSD are indicative of the accuracy and reproducibility of the method. The precision of the method was studied as an intraday; interday variations, and repeatability. The % RSD value < 2 indicates that the method is precise. Thus, the developed method is found to be robust and rugged which can be applied as a rapid tool for routine analysis of bazedoxifene acetate in the bulk and in the pharmaceutical dosage form.
Keywords: UV, Method development**,** Validation, Bazedoxifene acetate.

Introduction

Defined as a skeletal, degenerative bone disease, osteoporosis [1] occur in postmenopausal women, and prevalence increases with age [2]. Osteoporotic fractures account for substantial healthcare costs, disability, and mortality. Drug therapy plays a crucial role in both the prevention and treatment of osteoporosis when indicated. Recommended therapies include estrogen supplementation, bisphosphonates, recombinant parathyroid hormone, calcitonin, and selective estrogen receptor modulators (SERMs) [1, 2].

SERMs are a heterogeneous class of compounds that exert their pharmacologic effects at estrogen receptors (ERα and ERβ) [3]. A new SERM, bazedoxifene acetate, is currently under development in an effort to maximize potential benefits on bone, lipids, and breast tissue while minimizing endometrial hyperplasia and other adverse effects [4]. Such advancement in drug development may expand first-line treatment options for postmenopausal osteoporosis.

Bazedoxifene acetate (1*H*-Indol-5-ol,1-[[4-[2-(hexahydro-1*H*-azepin-1yl)eZthoxy] phenyl] methyl] 2-(4-hydroxyphenyl)-3methyl, WAY-140424) is a nonsteroidal, indole-based estrogen receptor ligand [5, 6]. Within the class of SERMs, chemical differences in the location and structure of side chains determine tissue selectivity, pharmacologic action, and lead to a mixed functional activity at the estrogen receptors [7]. Bazedoxifene binds to both ERα and ERβ with higher affinity toward ERα. Bazedoxifene exerts pharmacologic activity by binding to estrogen receptors in bone tissue as an agonist promoting preservation of bone mineral density (BMD). At breast and uterine tissue, bazedoxifene acts as an antagonist, therefore lacking stimulation and proliferative activity within these tissues [8].

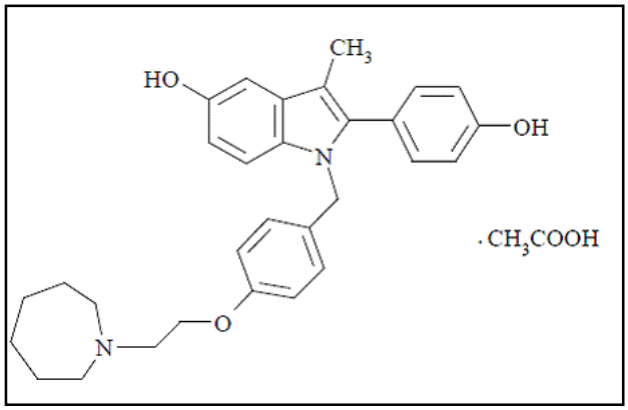

Fig. 1: Chemical structure of Bazedoxifene acetate

The aqueous solubility of bazedoxifene is poor with systemic exposure and extensive first pass metabolism. It has mean half life of 28 hrs and maximum concentration is reached in 1-2hrs after oral administration, it is mainly excreted by feces (84.7%) while renal excretion is negligible [9].

Bazedoxifene acetate is not yet official in any pharmacopeia, where, no analytical methods have been reported for its determination in bulk, pharmaceutical formulations and biological fluids.

Among the various methods available for the determination of drugs, spectrophotometry continues to be very popular, because of its simplicity, specificity, and low cost. Accordingly, the objective of this study was to develop and validate the UV-spectrophotometric method for the estimation of bazedoxifene acetate in bulk which can be applied to pharmaceutical formulations as per ICH guidelines.

Experimental

Bazedoxifene acetate was a gift sample from a MNC, Hyderabad. All chemicals and reagents used were of analytical grade and purchased from sd fine–chem. limited, Mumbai, India.

Preparation of standard stock solution

Accurately weighed 10 mg of Bazedoxifene acetate was transferred to a 100 mL volumetric flask, dissolved in 30 mL methanol by shaking manually until dissolved. The volume was adjusted with the same up to the mark to give the final strength, i.e., 100 µg/mL.

Selection of wavelength for analysis of bazedoxifene acetate

Accurately pipetted 1.0 mL volume of standard stock solution of bazedoxifene acetate was transferred into a 10 mL volumetric flask, diluted to a mark with distilled water to give concentration of 10 µg/mL. The resulting solution was scanned in the UV range (200–400 nm) using shimadzu UV- VIS spectrophotometer instrument (model no.8400S).

Validation of the method

The method was validated in terms of linearity, accuracy, precision, and ruggedness.

Linearity study

Different aliquots of bazedoxifene acetate in the range 0.2–1.0 mL were transferred into series of 10 mL volumetric flasks, and the volume was made up to the mark with distilled water to get concentrations 2, 4, 6, 8 and 10 µg/mL, respectively. The solutions were scanned on a spectrophotometer in the UV range 200–400 nm. The absorbance was recorded in methanol. The calibration plot was constructed as concentration *vs*. absorbance.

Accuracy

To the preanalysed sample solutions, a known amount of standard stock solution was added at different levels, i.e. 80%, 100%, and 120%. The solutions were reanalyzed by the proposed method.

Precision

Precision of the method was studied as intraday and interday variations. Intraday precision was determined by analyzing the 2, 6 and 10 µg/mL of bazedoxifene acetate solutions for three times in the same day. Interday precision was determined by analyzing the 2, 6, and 10 µg/mL of solutions daily for 3 days over the period of week.

Sensitivity

The sensitivity of measurements of bazedoxifene acetate by the use of the proposed method was estimated in terms of the limit of quantification (LOQ) and limit of detection (LOD). The LOQ and LOD were calculated using equation LOD = 3.3 × *N/B* and LOQ = 10 × *N/B*, where '*N*' is standard deviation of the absorbance values (n = 6), taken as a measure of noise, and '*B*' is the slope of the corresponding calibration curve.

Repeatability

Repeatability was determined by analyzing 6 µg/mL concentration of bazedoxifene acetate solution for six times.

Ruggedness

Ruggedness of the proposed method is determined for 6 µg/mL concentration of bazedoxifene acetate by analysis of aliquots from a homogenous slot by two analysts using same operational and environmental conditions.

Determination of bazedoxifene acetate in bulk

Accurately weighed 10 mg of bazedoxifene acetate was transferred into a 100 mL volumetric flask containing 30 mL methanol, and the volume was made up to the mark using the same. Appropriate volume 0.6 mL of this solution was transferred to a 10 mL volumetric flask, and the volume was adjusted to the mark using methanol. The resulting solution was scanned on a spectrophotometer in the UV range 200–400 nm. The concentration of the drug was calculated from linear regression equations.

Results and Discussion

Bazedoxifene acetate showed absorbance maximum at 298 nm in methanol [Fig 2] and 299nm in SGF [Fig 3].

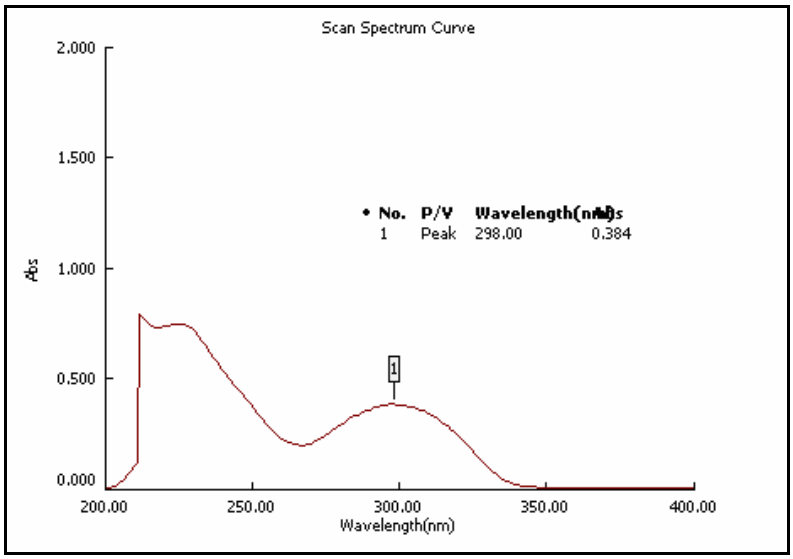

Fig. 2: UV spectrum of Bazedoxifene acetate in methanol

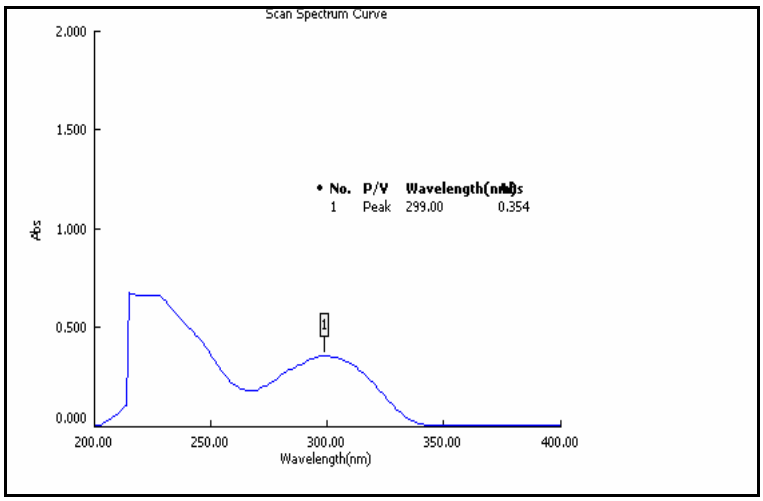

Fig. 3: UV spectrum of Bazedoxifene acetate in SGF.

Method validation

The proposed method was validated as per ICH guidelines [10]. The solutions of the drugs were prepared as per the earlier adopted procedure given under methods section.

Linearity studies

The linear regression data for the calibration curves showed good linear relationship over the concentration range 2–10 µg/mL for bazedoxifene acetate in methanol [Fig 4]. The results are expressed in Table 1. The correlation coefficient is found to be 0.995, which meet the method validation acceptance criteria and hence the method is said to be linear.

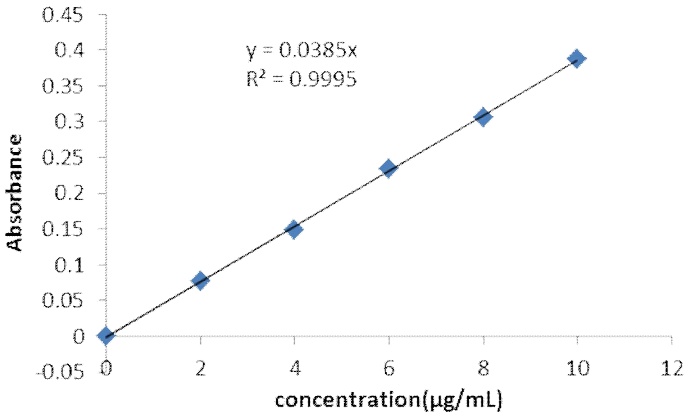

Fig. 4: Calibration curve of Bazedoxifene acetate in methanol

Table 1: Linearity study of Bazedoxifene acetate

Concentration (µg/mL)	Absorbance* (Mean±SD)	%RSD
2	0.0746±0.001	1.52
4	0.1478±0.001	0.88
6	0.235±0.0008	0.35
8	0.3072±0.001	0.42
10	0.387±0.001	0.40

*Average of Five determinations

Accuracy

The solutions were reanalyzed by the proposed method; results of recovery studies are reported in Table 2 which showed that the % amount found was between 97.00% and 99.83% with % RSD < 2. % Relative standard deviation values less than 2 indicate good recovery values and hence the accuracy of the method developed.

Table 2: Recovery studies

Pre- analyzed sample solution (µg/mL)	Amount of drug added (µg/mL)	Amount recovered*(µg/mL)	% Recovery	%RSD
6	0	5.99	99.83	1.54
	4.8	10.72	99.25	0.98
	6.0	11.64	97.00	1.46
	7.2	13.05	98.86	1.72

*average of three determinations

Precision

The precision of the developed method was expressed in terms of % relative standard deviation (% RSD). These results show reproducibility of the assay. The % RSD values found to be less than 2 that indicate the method is precise [Table 3].

Table 3: Precision Studies

Component	Concentration (µg/mL)	Intraday Precision (n=3)		Interday Precision (n=3)	
		Conc. Found (µg/mL)	%RSD	Conc. Found (µg/mL)	%RSD
Bazedoxifene acetate	4	3.9	1.3	4.1	1.2
	6	6.2	1.7	6.1	0.7
	8	7.9	0.8	8.1	0.9

Sensitivity

The linearity equation was found to be $Y = 0.038X - 0.0024$. The LOQ and LOD for bazedoxifene acetate were found to be 0.085µg and 0.25µg, respectively. The values from the result clearly indicate the sensitivity of the developed method.

Repeatability

Repeatability was determined by analyzing 6 µg/mL concentration of bazedoxifene acetate solution for six times and the % amount found was between 98.21% and 100.76% with % RSD < 2 [Table 4]. The closeness of the obtained results indicates the reproducibility of the developed method.

Table 4: Repeatability studies

Component	Amount taken(µg/mL)	Amount found* (%)	%RSD
Bazedoxifene acetate	6	99.77	0.92

*average of six determinations

Ruggedness

The absorbance was measured by two analysts. The results are in the acceptable range and given in [Table 5]. The result showed that the % RSD is less than 2 hence the method is rugged.

Table 5: Ruggedness Studies

Component	Amount taken(µg/mL)	Amount found n=3 (%)	
Bazedoxifene acetate	6	**Analyst I ± SD**	**Analyst II ± SD**
		99.21 ± 1.43	99.14 ± 1.2

Determination of bazedoxifene acetate in bulk

The concentrations of the drug were calculated from linear regression equations. The % amount found was between 96% and 99% [Table 6]. The results indicate that the method can be applied to the routine quality control and stability studies.

Table 6: Analysis of Bazedoxifene acetate in bulk

Concentration (µg/mL)	Amount found* (µg)	Amount found* (%)
6	5.89	98.16
	5.87	97.83
	5.94	99.00
	5.91	98.50
	5.76	96.00
	5.92	98.66
Mean ± SD	5.88 ± 0.06	98.02 ± 1.07
% RSD	1.09	1.09

*average of six determinations

Conclusion

The developed UV-spectrophotometric technique is quite simple, accurate, precise, reproducible, and sensitive. Application of the proposed method for pharmaceutical formulation was not possible as the drug in the form of formulation is not available in India yet. But the validation procedure confirms that this is an appropriate method which can be applied to quantification in the formulation. It can also be extended to routine quality control of the formulations containing this entire compound.

Acknowledgements

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