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SPECTROPHOTOMETRIC METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF TEDIZOLID PHOSPHATE BY HYDROTROPY

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ABSTRACT

This study focuses on the development and validation of a spectrophotometric method for the estimation of tedizolid phosphate using hydrotropy. The developed method utilizes the principle of hydrotropy, a solubilization technique, to enhance the solubility and subsequent estimation of tedizolid phosphate. Sodium benzoate was selected as the hydrotropic agent, which effectively increases the solubility of tedizolid phosphate in the aqueous medium. The solubility enhancement property of sodium benzoate enables the spectrophotometric estimation of tedizolid phosphate at a specific wavelength. Several parameters of the spectrophotometric method were optimized, including the concentration of sodium benzoate, wavelength selection, and linearity range. The method was validated according to International Conference on Harmonization (ICH) guidelines for parameters such as accuracy, precision, linearity, specificity, and robustness. The validation results confirmed the reliability and suitability of the developed method for the estimation of tedizolid phosphate. The proposed spectrophotometric method demonstrated good linearity over the concentration range of 10-50µg/mL. The developed method exhibited satisfactory accuracy, precision, and specificity. The robustness of the method was also evaluated by introducing deliberate variations in experimental conditions, and the results confirmed its robust nature. In conclusion, the developed spectrophotometric method utilizing hydrotropy for the estimation of tedizolid phosphate provides a simple, accurate, and cost-effective approach for routine analysis in pharmaceutical industries. The validated method can be utilized for the quality control and assessment of tedizolid phosphate formulations, ensuring their safety and efficacy.

Key words: Spectrophotometric method, Tedizolid phosphate, Hydrotropy, Method development, Validation

INTRODUCTION

Drugs used for the treatment of ocular disorders often have low aqueous solubility and eye drops are only in contact with ocular tissue for a short time. Formulations that are developed to increase the amount of available drug in solution could improve its bioavailability; therefore, solubility enhancement is an important tant strategy to use when developing ocular medication. An approach taken by scientists was to take the poorly soluble drug, indomethacin, and convert this drug into its sodium salt.

They found that this improved its aqueous solubility and the drug was stable at physiological pH and compatible with excipients used for ocular drug formulation (Coffman *et al.*, 2002).

Solubility enhancement can be achieved by employing hydrotropic compounds. Researchers reported the effectiveness of caffeine, urea and nicotinamide and its derivatives as efficient hydrotropes for enhancing the solubility of riboflavin, a vitamin with poor aqueous solubility of less than 0.1 mg/ml-1, which is used as a photosensitive drug for the treatment of keratoconus. Cyclodextrins are a class of cyclic supramolecular compounds that have been well studied for dissolution enhancement of low solubility drugs; Loftsson and Stefansson discussed the use of cyclodextrins for complexation with steroids, carbonic anhydrase inhibitors, pilocarpine and cyclosporins in eye drop formulations that are well tolerated. Cyclodextrins for their hydrotropic properties were also investigated and were able to show that β-cyclodextrin achieved solubility enhancement of more than 140% for riboflavin., N, N-diethylnicotinamide (DENA) and N, N-dimethylbenzamide (DMBA), with 13 poorly water-soluble drugs and these compounds were shown to have superior hydrotropic action – between 1000- and 10,000-fold (Loftsson and Stafansson, 2002).

The proto-type sodium benzoate, a standard Neuberg's hydrotropic salt, has a chemical structure that mostly consists of an anionic group and a hydrophobic aromatic ring or ring system. It is clear that the anionic group contributes to the high aqueous solubility required for a material to be hydrotropic. The type of metal ion or anion seemed to have just a small influence on the event. Alkali metal salts of various organic acids make up the solute. Ionic organic salts are hydrotropic agents. The solute is said to be "salted in" by additives or salts that improve solubility in a particular solvent, and "salted out" by additives or salts that decrease solubility. The phenomenon known as "hydrotropism" refers to the "salting in" of non-electrolytes caused by a number of salts with big anions or cations that are also extremely soluble in water. The contact between the hydrotropic agent and the solute in hydrotropic solutions is weak and they do not exhibit colloidal characteristics (Liu and Guo, 2005; Khan & Singh, 2016).

The term hydrotropic has been used to designate the increase in solubility of poorly water soluble drugs in concentrated solutions of hydrotropic agents .A huge number of poorly water soluble drugs have been solubilized by use of various hydrotropic solutions. Sodium salicylate, Sodium benzoate, nicotinamide, urea, sodium ascorbate, sodium ascorbate, sodium citrate, sodium acetate are the most commonly used hydrotropic agents. Thiourea have been employed to increase solubility of poorly water soluble drug various organic solvents like methanol, chloroform, alcohol have been used for solublisation of poorly water soluble drugs. Drawbacks of Organic solvents include higher cost, toxicity, pollution and error, in analysis due to volatility

The primary aim of this study was to employ hydrotropic solubilizing agents to enhance solubility of poor water soluble drug like tedizolid phosphate and to avoid use of organic solvents.

This hydrotropic solution did not interfere in method development. This method statistically validated as per ICH guidelines.

MATERIALS AND METHODS

Determination of solubility enhancement by UV/ Vis. spectroscopy

Solubility studies were performed in distilled water 2M Sodium acetate, 8M Urea, 2M Sodium Citrate, 2M Sodium Benzoate, 2M Ammonium Acetate, 2M Sod. Citrate, 2M Sodium acetate: 2M Sodium Benzoate, 2M Urea: 2M Sodium acetate, 2M Sodium citrate: 8M Urea, 2M Sodium citrate:8M Urea, 2M Ammonium Acetate: 2M Sod. Citrate at room temperature (25 ± 2^0 C). An excess amount of drug was added to 100ml of solvent in screw-capped glass vials; these were mechanically shaken for 48 hours at 25°C until equilibrium was achieved. Aliquots were withdrawn, filtered through a membrane filter (0.45µ) and spectrophotometrically analyzed for solubility. Enhancement of solubility was more than 60 to 70 % for Tedizolid phosphate respectively in mixed hydrotropic solution, 2M Ammonium Acetate: 2M Sod. citrate (1:1). The enhancement of solubility of Tedizolid phosphate due to the hydrotropic solubilization phenomenon.

Establishment of stability profile

Stability of both drugs was observed by dissolving Tedizolid phosphate in 2M Ammonium Acetate: 2M Sod. Citrate (1:1) solution used as solvent. Solution of Tedizolid phosphate was prepared in the conc. of 5 µg/ml and 10 µg/ml respectively and scanned under time scan for 30 min. Spectra of both drugs under time scan shows that of both drugs are stable in mixed hydrotropic solution.

Linearity range and calibration graph

Preparation of Standard Stock Solution (Stock-A)

Standard stock solutions were prepared by dissolving separately 100 mg of each drug in 80`mL mixed hydrotropic solution containing 2M Ammonium Acetate: 2M Sod. Citrate (1:1) and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to 100ml with mixed hydrotropic agent to get a concentration of 1000 µg/ml (Stock-A) for both drugs.

Preparation *of Sub Stock Solution (Stock-B)*

Aliquots of 2.5 ml withdrawn with help of pipette from standard stock solution A of Tedizolid phosphate and transferred into 25 ml volumetric flask separately and diluted up to 25 ml with 2M Ammonium Acetate: 2M Sod. Citrate (1:1) that gave concentration of 100 µg/ml (Stock-B).

Preparation of Working Standard Solution

Aliquots of 1.0 ml, 2.0 ml, 3.0 ml, 4.0 ml and 5.0 ml withdrawn with help of pipette from standard stock solution (Stock-B) separately in 10 ml volumetric flask and volume was made up to 10 ml with 2M Ammonium Acetate: 2M Sod. Citrate (1:1). This gave the solutions of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml and 50µg/ml respectively for 2M Ammonium Acetate: 2M Sod. Citrate (1:1).

Selection of wavelength for linearity

Solution of 10 µg/ml Tedizolid phosphate were prepared separately the solutions were scanned in the spectrum mode from 200 nm to 400 nm. The maximum absorbance of Tedizolid phosphate was observed at 256 nm respectively. Tedizolid phosphate showed linearity in the concentration range of 10-50µg/ml Calibration curve was plotted, absorbance versus concentration.

Validation of simultaneous equation method

Linearity

Linearity of both drugs was established by response ratios of drugs. Response ratio of drug calculated by dividing the absorbance with respective concentration. Then a graph was plotted between concentration and response ratio.

Accuracy

The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e. 80%, 100%, 120%. The recovery studies were carried out by adding known amount of standard solution of Tedizolid phosphate to preanalysed tablet powder. The resulting solutions were then re-analysed by proposed methods. Whole analysis procedure was repeated to find out the recovery of the added drug sample. This recovery analysis was repeated at 3 replicate of 5 concentrations levels.

Precision

Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to Day and analyst to analyst) and reproducibility. Repeatability was performed by analyzing same concentration of drugs for five times. Day to Day was performed by analyzing 5 different concentration of the drug for three days in a week.

Analysis of tablet sample

Twenty marketed tablets of TDZ were weighed and ground to a fine powder; amount equal to 10mg of TDZ was taken in 10 ml volumetric flask. Then 8 ml of 2M Ammonium Acetate: 2M Sod. Citrate (1:1) solution was added and the flask was sonicated for about 10 min to solubilize the drug present in tablet powder and the volume was made up to the mark with hydrotropic solution. After sonication filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with distilled water to get the final concentrations of both drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from simultaneous equation method. The procedure was repeated for five times.

Analysis of tablet sample

Twenty marketed tablets of TDZ were weighed and ground to a fine powder; amount equal to 10mg of TDZ was taken in 10 ml volumetric flask. Then 8 ml of 2M Ammonium Acetate: 2M Sod. Citrate (1:1) solution was added and the flask was sonicated for about 10 min to solubilize the drug present in tablet powder and the volume was made up to the mark with hydrotropic solution. After sonication filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with distilled water to get the final concentrations of both drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from simultaneous equation method. The procedure was repeated for five times.

Table 1: Results of Linearity of Tedizolid phosphate (TDZ)

	Results of Linearity
Parameter	**TDZ**
Working λ_{max}	256nm
Beer's law limit (µg/ml)	10-50
Correlation Coefficient (r^2)*	0.995
Slope (m)*	0.020
Intercept (c)*	0.023

*Average of five determination

Table 2: Results of recovery studies on marketed formulations

Recovery Level %	% Recovery (Mean±SD)*
80	98.79±0.641
100	99.07±0.183
120	98.97±0.980

Table 3: Results of validation

Parameter		
Precision (%R.S.D.)*	Repeatability	98.970±0.098
	Day to Day	98.892±0.114
	Analyst to Analyst	98.964±0.171
	Reproducibility	98.960±0.221

*Average of five determination

Table 4: Analysis of tablet sample

Drug	Label claim (mg)	Amount found (mg)	Label claim (%)	S.D.	% RSD
TDZ	200	199.15	99.57	0.165	0.182

RESULTS AND DISCUSSION

Based on the solubility, stability and spectral characteristics of the drugs, 2M Ammonium Acetate: 2M Sod. Citrate (1:1) solution was selected as hydrotropic agent. Presence of hydrotropic agent do not shows any significant interference in the spectrophotometric assay thus further confirming the applicability and reproducibility of the developed method.

The developed methods were found to be linear (Table 1). The values of mean percent recoveries were found to shown in Table 2 and results of validation were shown in Table 3.

The mean percent label claims of tablets by the proposed methods were close to 100, indicating the accuracy of the proposed method and low values of standard deviation, percent coefficient of variation and standard error further validated the proposed method.

CONCLUSION

The result obtained shows the developed method to be precise, simple, rapid and accurate. Thus these can be used for routine analysis of Tedizolid phosphate in bulk drug. It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration. Spectrophotometric precluding the use of organic solvents and thus avoids the problem of residual toxicity, error due to volatility, pollution, cost etc.

It was thus, concluded that the proposed method is new, simple, accurate, safe, free form pollution, precise and can be successfully employed in the routine analysis. The simplicity, rapidity reproducibility and economy of the proposed methods completely fulfill the objective of this research work.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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