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Short Communication

Selective spectrophotometric determination of diltiazem hydrochloride in tablets

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Introduction

Diltiazem hydrochloride (**Ia**) is an important coronary vasodilator drug of the calcium channel-blocker type, used in therapy of heart disease and hypertension. The compound is (+)-5-[2-(dimethylamino)ethyl]-*cis*, 2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate monohydrochloride. The drug and its tablet formulations are official in the USP [1] wherein they are estimated by an HPLC method. The other methods for its estimation include GC [2, 3] HPLC [4, 5] and titrimetry [6].

The ferric hydroxamate method is one of the most widely used methods in spectrophotometric analysis of drugs with an ester functionality [7–11]. Diltiazem hydrochloride contains an acetate moiety and hence is amenable to quantification by the above method. The present work describes the optimization of conditions for the determination of diltiazem in its tablet formulation by the ferric hydroxamate method.

Experimental

Instrumentation

All spectral and absorbance measurements were made on a Shimadzu (UV-260) UV–vis Spectrophotometer with 1 cm matched quartz cells.

Chemicals

All chemicals used were of AR grade. Diltiazem hydrochloride and desacetyl diltiazem hydrochloride reference standards were obtained from M/s Orion Co. Ltd (Finland).

Hydroxylamine reagent. An aqueous solution was prepared by mixing equal volumes of 12.5% (w/v) hydroxylamine hydrochloride and 12.5% (w/v) of sodium hydroxide.

Ferric reagent. A 1.25 g mass of ferric ammonium sulphate was dissolved in 10 ml of perchloric acid 70% (w/w) and diluted to 100 ml with distilled water.

Dilute perchloric acid solution. A 14% solution (w/v) was prepared by diluting 10 g of 70% (w/w) solution to 50 ml with water.

Standard stock solution. A 100 mg mass of diltiazem hydrochloride was dissolved in 25 ml of methanol.

Procedure for the calibration curve

Into a series of 25 ml volumetric flasks different volumes of drug solution (4 mg ml^{-1}; 1–5 ml) were pipetted. The total volume was adjusted to 5 ml in all the flasks with methanol. To each flask 3 ml of hydroxylamine reagent was added and the solutions were kept at 72 ± 0.5°C in a constant temperature water bath. After 20 min, the solutions were cooled to room temperature. To each flask 1 ml of ferric reagent and 2 ml of dilute perchloric acid solutions were added with shaking. The volume was made up to the mark with methanol and absorbance was measured within 5 min at 500 nm against a reagent blank.

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Results and Discussion

An organic ester is known to react with hydroxylamine in alkaline medium [7, 10] to form a hydroxamic acid, which combines with ferric ions under suitable conditions to form a characteristic red to purple chelate:

$$CH_3—CO—OR + NH_2OH.HCl + NaOH \rightarrow CH_3—CO—NHOH + ROH + NaCl + H_2O$$

$$CH_3—CO—NHOH + FeCl_3 \rightarrow Fe(CH_3—CO—NHO)^{2+} + Cl^- + H^+$$

$$\uparrow\downarrow$$

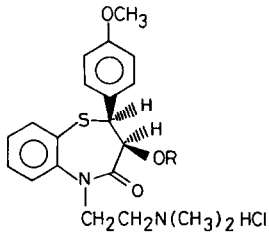
$$Fe(CH_3—CO—NHO)_2^+$$

$$\uparrow\downarrow$$

$$Fe(CH_3—CO—NHO)_3$$

Scheme 1

Diltiazem hydrochloride (**Ia**) contains an acetate moiety and therefore was found to undergo similar reactions to furnish a purple coloured ferric hydroxamate complex that can be measured spectrophotometrically. Since this reaction is specific for the acetate group, desacetyl diltiazem hydrochloride (**Ib**) if present in the formulation is not likely to interfere.



I a R = $COCH_3$
I b R = H

Optimization of colour development conditions

Temperature. The reaction of diltiazem with alkaline hydroxylamine was studied at 30, 50, 70, 80 and 90°C. It was found that maximum colour development occurred at 70°C. Further experiments were performed in the temperature range of 70–72°C.

Reaction time. An investigation of the effect of reaction time showed that maximum colour was obtained when the reaction between hydroxylamine and diltiazem was carried out at 70–72°C for about 20 min. Also the intensity of the colour rose to a maximum within 2 min after the addition of the ferric reagent and remained constant for another 3 min after which it gradually declined. Therefore, all absorbance measurements were made at about 4 min after the addition of the ferric reagent.

Solvent. The reaction was carried out using four solvents, namely methanol, ethanol, isopropanol and water. On the basis of solubility of the drug and optimal stability and intensity of the colour, methanol solution of the drug was used for further experiments.

pH of the reaction. The effect of pH was investigated by using hydroxylamine reagent containing different amounts of sodium hydroxide. Experiments at pH 8.0, 10.0, 12.0, 13.0 and 13.8 showed that maximum colour intensity was obtained at pH 13.8. This may be ascribed to the increase in the rate of hydrolysis and also a shift in the ratio of the three coloured species as the pH was increased from 8.0 to 13.8 (Scheme 1).

The second variable in colour development was the amount of excess of acid desirable over that necessary to neutralize the sodium hydroxide required for hydrolysis. An investigation of the effect of acidity showed that at low acidities the colour was marginally more intense and the colour was more stable. A 2 ml volume of perchloric acid 14% (w/v) was found to be optimum for the purpose.

Under the optimized conditions the absorption spectrum of the complex showed a maximum at 500 nm with molar absorptivity 0.485×10^3 l mol^{-1} cm^{-1} on the basis of the molecular weight of diltiazem hydrochloride. By following the procedure described above, absorbance measurements of the standard drug solutions were made at 500 nm and a calibration curve was constructed by plotting absorbance versus concentration of the drug in $\mu g\ ml^{-1}$. The curve was linear in the range of 50–800 $\mu g\ ml^{-1}$. The intercept was 0.1390 with a correlation coefficient of 0.9993.

Table 1
Results of diltiazem tablet analysis

Formulation	Labelled amount of diltiazem HCl (mg)	Amount found* (mg)	Recovery (%)
Tablet A	30	29.62	98.73
Tablet B	30	30.02	100.07
Tablet C	60	58.72	97.87
Tablet D	60	59.60	99.33

* Average of eight experiments.

Analysis of tablets

Twenty tablets were weighed and powdered. A quantity of powder equivalent to 60 mg of drug was transferred to a dry beaker. The drug content was extracted with 60 ml chloroform in two or three instalments. The filter was washed with 10 ml chloroform. The combined filtrate was evaporated to dryness and the residue was dissolved in 50 ml of methanol. A 5 ml volume of filtrate was used for the colour development by the described method. The amount of drug corresponding to the absorbance value was found from the calibration graph and the content of diltiazem hydrochloride in a tablet calculated using the dilution factor. The results are given in Table 1.

Interference

Common excipients found in the tablet formulation showed no interference. Moreover, desacetyl diltiazem hydrochloride and acetic acid, the products of hydrolysis of the drug, also showed no interference. Interference studies were carried out both with standard reference samples of desacetyl diltiazem hydrochloride and acetic acid and also partially hydrolysed drug sample.

Reproducibility and recovery

A 5 ml volume of diltiazem hydrochloride solution (1 mg ml^{-1}) was placed in each of six 25 ml flasks. The colour was developed as described under procedure for the calibration curve. The absorbance values were found to be reproducible with a relative standard deviation of 0.72%. For recovery studies 3 ml of standard drug solution were added to 3 ml of tablet solution which had been analysed earlier. The colour of the solution was developed together with that of 6 ml of standard diltiazem solution. The recovery of the drug was 98.95–100.86%.

Conclusion

The above results show that the present method is simple for the analysis of diltiazem hydrochloride and insensitive to products of its hydrolysis. The method is thus suitable for the routine analysis of diltiazem tablets and can serve as an alternative to the official USP method.

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