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ORIGINAL ARTICLE

Spectrophotometric microdetermination of anti-Parkinsonian and antiviral drug amantadine HCl in pure and in dosage forms

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Abstract Two simple, rapid, sensitive, low-cost, and accurate methods (A and B) for the microdetermination of amantadine HCl (AMD) in pure form and in pharmaceutical formulations are developed. Method A is based on the formation of tris (*o*-phenanthroline)-iron(II) complex (ferroin) upon reaction of amantadine HCl with an iron (III)-*o*-phenanthroline mixture in sodium acetate-acetic acid buffer media. The ferroin complex is spectrophotometrically measured at λ_{max} 509 nm against reagent blank. Method B is based on the reduction of Fe (III) by the drug which forms colored complex (λ_{max} 521 nm) with 2,2′-bipyridyl. Optimizations of the experimental conditions are described. Beer's law is obeyed in the concentration ranges 0.4–10 and 0.6–22 μg mL^{-1} using 1,10-phenanthroline and 2,2′-bipyridyl, respectively. The developed methods have been successfully applied for the determination of AMD in bulk drugs and in pharmaceutical formulations. The common excipients and additives did not interfere in their determinations.

1. Introduction

Amantadine HCl chemically as 1-adamantanamine hydrochloride, or known formally as 1-aminoadamantane hydrochloride. The molecule consists of adamantane backbone that is substituted at one of the four methyne positions with an amino group. This compound is sold under the name "Symmetrel" for use both as an antiviral and an antiparkinsonian drug, against Asian influenza and eventually received approval for the treatment of Influenza virus A (Moiseev et al., 1976; Maugh, 1979; Hounshell and Smith, 1988) in adults, issued an alert to doctors not to prescribe amantadine any more for the season. Among some Asian countries, A/H3N2 and A/H1N1 resistance has reached 100% (Varough et al., 2007). Amantadine hydrochloride (AMD), Scheme 1, is an antiviral agent used against infection with influenza type A virus and to ameliorate symptoms when administered during the early stages of infection as well as in the management of herpes zoster (Prud'homme et al., 1997). It has mild anti-Parkinsonism activity and thus it has been used in the management of Parkinsonism, mainly in the early disease stage and

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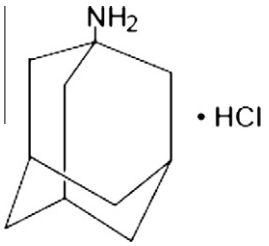

Scheme 1 Amantadine hydrochloride (AMD).

when the symptoms are mild. AMD is usually given by mouth as the hydrochloride salt (Martindale, 2002).

Spectrophotometry is considered as the most convenient analytical technique in pharmaceutical analysis because of its inherent simplicity and availability in most quality control and clinical laboratories (Amin et al., 2009, 2008). However, AMD does not possess any chromophore in its molecule, which are the essential requirements for the direct analysis by spectrophotometric techniques. Therefore, derivatization of AMD was necessary for its determination. For spectrophotometric determination of AMD, it has been derivatized with different reagents. The involved derivatization reactions that have been published prior to 1983 have been reviewed (Kirschbaum, 1983). The derivatizing reagents used thereafter included iodine (Darwish et al., 2006), acetaldehyde/chloranil (Darwish et al., 2006), α,α-diphenyl-β-picrylhydrazyl (Salman and Bayrakdur, 1983), bromocresol green (Sultan, 2004), tetracyanoethylene (Rizk et al., 2003), iron(III) (Mustafa et al., 2004), and cyclodextrin, Kuwabara et al., 1999). As well, many derivatization techniques coupled with chromatography have been established for the determination of AMD in the dosage forms and biological matrices: TLC (Askal et al., 2008), HPLC (Duh et al., 2005; Higashi et al., 2006), GC (Leis et al., 2002), and capillary electrophoresis (Reichová et al., 2002).

Redox reactions have been used as the basis for the development of simple and sensitive spectrophotometric methods for the determination of many pharmaceutical compounds (Amin et al., 2003; Shama et al., 2006, 2009; El-Didamoony et al., 2006). For these reasons, these reactions were attempted for use in the present study. In oxidimetric reactions, the most commonly used oxidizing agents is Fe(III) whish reduced to Fe(II), and then determined with either 1,10-phenanthroline or 2,2′-bipyridyl. None of these reagents have not been previously used for the spectrophotmetric analysis of amantadine HCl. For these reasons, the present study was dedicated to investigate the application of these reagents in the spectrophotometric analysis of AMD in their pharmaceutical dosage forms and spiked plasma samples. The proposed methods were used for quality control analysis, where modern and expensive apparatus such as GLC, HPLC and HPTLC are not available.

2. Experimental

2.1. Apparatus

All the spectral measurements were made using either Perkin–Elemer Lambda 12 and Perkin–Elemer 73B spectrophotometers, with scanning speed 400 nm/min and band width 2.0 nm, equipped with 10 mm matched quartz cells and a Metrohm (Switzerland) pH-meter were used for spectrophotometric pH measurements. A thermostat water bath, JOUAN, J18 Bain Universal (France) was used to carry out the temperature studies.

2.2. Material and reagents

All chemicals used were of analytical grade and all solutions were freshly prepared in doubly distilled water.

(1) Pure amantadine HCl bulk powder was obtained from Egyptian Organization for Control and Pharmaceutical Research – Egypt. Amantadine HCl working solution prepared by dissolving 0.01 g of pure AMD in 50 mL of bidistilled water and complete to 100 ml with bidistilled water to obtain the working standard solution of concentration 100 μg mL^{-1}.
(2) Preparation of Fe(III)-*o*-phenanthroline reagent (Mahrous, 1991). Mix 0.198 g of 1,10-phenanthroline monohydrate (Fluka, Swiss) with 2.0 mL of 1.0 M HCl and 0.16 g of ferric ammonium sulphate dodecahydrate (Fluka, Swiss) and dilute with bidistilled water to 100 mL.
(3) Preparation of Fe(III)-bipyridyl reagent (Mahrous, 1991) (Hapkin & Williams, England), dissolve 0.16 g of 2,2′-bipyridyl in 2.0 mL of 1.0 M HCl and 0.16 g of ferric ammonium sulphate dodecahydrate.
(4) Acetate buffer solutions were prepared as recommended previously (Britton, 1952).

2.3. General procedure for bulk powder

Aliquots (0.03–1.0 mL) and (0.06–2.2 mL) of 100 μg mL^{-1} AMD standard solution were transferred for Methods A and B, respectively, into a series of 10 mL calibrated flasks; 1.6 mL Fe^{3+}-*o*-phen (Method A) or 1.1 mL Fe^{3+}-bipy (Method B) reagent solution and 2.0 mL of pH 4.3 (method A) or 3.0 mL of pH 4.16 (method B) acetate buffer solution were added and heated on a water bath at 70 °C for 10 min. The mixture was cooled to room temperature (25 ± 1 °C), and the volume was diluted to the mark with double-distilled water. The colored complexes formed were measured at 509 and 521 nm for methods A and B, respectively, against a reagent blank treated similarly.

2.4. Capsules sample solution

Twenty capsules were carefully evacuated; their contents were weighed and finely powdered. An accurately weighed quantity of the capsule contents equivalent to 100 mg of AMD was transferred into a 100 mL calibrated flask, and dissolved in about 40 mL of distilled water. The contents of the flask were swirled, sonicated for 5.0 min, and then completed to volume with water. The contents were mixed well and filtered rejecting the first portion of the filtrate. The prepared solution was diluted quantitatively with distilled water to obtain a suitable concentration for the analysis.

2.5. Spiked plasma samples

Aliquots of 1.0 mL of plasma were spiked with different concentration levels of AMD. The spiked plasma samples were

treated with 0.1 mL of 70% perchloric acid and vortexed for 1.0 min. The samples were centrifuged for 20 min at 13000 rpm. The supernatants were transferred into test tubes and neutralized with 1.0 M NaOH solution.

3. Results and discussion

Ferric salts play a prominent role in the spectrophotometric determination of many pharmaceutical drugs, acting as an oxidant, a ferric salt gets reduced to ferrous salt and this amount corresponds to drug concentration. The amount of Fe(II) can be determined using selective reagents such as 1,10-phenanthroline and 2,2′-bipyridyl. These properties have been utilized to develop a spectrophotometric methods for the determination of AMD. 1,10-phenanthroline and 2,2′-bipyridyl are organic bases with similar chemical structure and contain the iron (II) specific group (Marczenko, 1976).

The proposed methods A and B are based on the formation of tris (*o*-phenanthroline) or tris(2,2-bipyridyl)-iron(II) chelate upon the reaction of AMD with an iron (III)-*o*-phenanthroline or iron (III)-2,2′-bipyridyl reagent. The reaction proceeds through reduction of iron(III) ions to iron(II) and subsequent formation of the intensive orange-red colored complex.

The absorption spectra of the colored complexes in the proposed methods showed a characteristic λ_{max} values as in (Fig. 1). The experimental conditions were established by varying each parameter individually (Massart et al., 1988).

3.1. Effect of pH

An acetate buffer solution was optimal among those examined (universal, phosphate, thiel, borate, and acetate). pH adjustment is necessary, especially in acidic medium, because the reaction was affected by change of pH in the range of (2.5–5.6). The optimum pH value was 4.3 for method A, and 4.14 is the optimum for method B. Moreover, 2.0 mL buffer solution was sufficient for method A, whereas 3.0 mL is the best for method B, for complete color development (Fig. 2).

3.2. Effect of reagent concentration

The addition of 1.6 mL of Fe^{3+}-*o*-phen or 1.1 mL of Fe^{3+}-bipy reagent was sufficient to obtain the maximum and reproducible

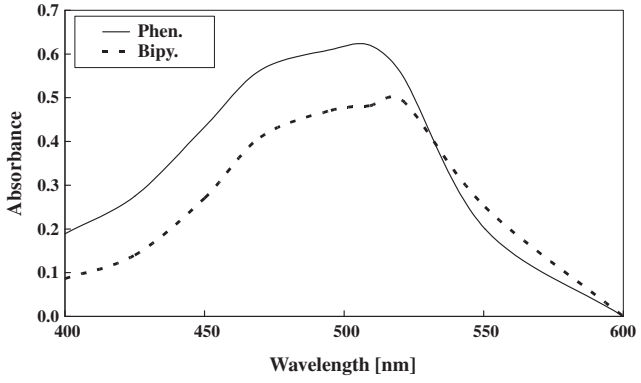

Figure 1 Absorption spectra for the colored comples of 6.0 μg mL^{-1} of AMD for method A (phen.) and 10.0 μg mL^{-1} for method B (bipy.).

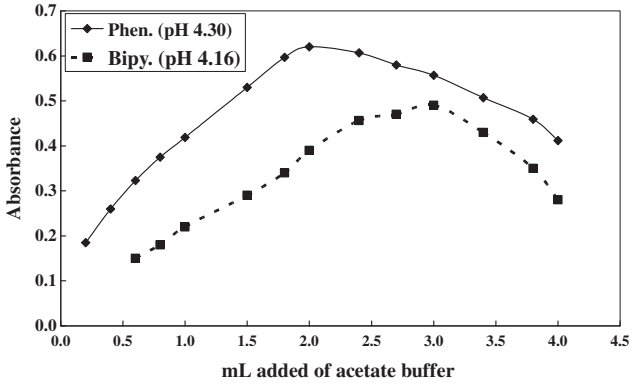

Figure 2 Effect of ml added of acetate buffer on absorbance of 6.0 μg mL^{-1} of AMD for method A (phen.) and 10.0 μg mL^{-1} for method B (bipy.).

absorbance for the studied complexes. Smaller amounts gave incomplete complex formation. A larger concentration had no effect on complex formation, although the absorbance increased slightly due to the background of the reagent used.

3.3. Effect of temperature and heating time

The effects of temperature and heating time on the formation of the colored complexes were studied. The reaction of AMD with both reagents proceeds very slowly at room temperature. Higher temperature was used to accelerate the reaction. Maximum absorbance was obtained after heating for about 10 min with both Fe^{2+}-phen and Fe^{2+}-bipy colored complexes on a water bath at 70 °C. At lower temperature, the rate of color development becomes progressively slower. Further heating caused no appreciable change in the color. The obtained complex was stable for more than 48 h.

3.4. Validation of the proposed methods

3.4.1. Calibration curves, linearity and sensitivity

Under the optimum reaction conditions described above, the calibration curves for AMD using the proposed methods employed in the present work were constructed. The regression equations for the results were derived using the least squares method. In all cases, Beer's law plots ($n = 6$) were linear with very small intercepts and good correlation coefficients in the general concentration range of 0.4–10.0 and 0.6–22.0 μg mL^{-1}, using method A and B, respectively (Table 1). For more accurate analysis, Ringbom optimum concentration range were evaluated to be 0.7–9.60 and 1.0–21.2 μg mL^{-1}, respectively (Table 1).

Statistical analysis of the results obtained (Table 1), indicated that the proposed methods were accurate and precise. The limits of detection (LOD) and limits of quantitation (LOQ) were determined (Irving et al., 1981) using the formula:

$$\text{LOD or LOQ} = \kappa SD_a/b,$$

where $\kappa = 3$ for LOD and 10 for LOQ, SD_a is the standard deviation of the intercept, and b is the slope. Based on the basis of six replicate measurements, the limits of detection were 0.12, and 0.18 μg mL^{-1} and the limits of quantification were 0.39,

Table 1 Analytical characteristics of the proposed methods.

Parameter	Methods	
	Fe^{2+}-phen	Fe^{2+}-bipy
pH (acetate buffer)	4.30	4.16
λ_{max} (nm)	509	521
Stability/h	48	48
Beer's conc. range (μg mL^{-1})	0.4–10.0	0.6–22.0
Ringbom optimum range (μg mL^{-1})	0.7–9.6	1.0–21.2
Detection limits (ng mL^{-1})	0.12	0.58
Quantification limits (μg mL^{-1})	0.39	0.373
Molar absorptivity (L mol^{-1} cm^{-1})	1.92×10^4	0.91×10^4
Sandell sensitivity (ng cm^{-2})	9.8	20.7
Regression equation[a]		
Slope	0.1023	0.0483
RSD% of slope	0.0091	0.0063
Intercept	0.0081	−0.0018
Correlation coefficient	0.9996	0.9994
RSD%	1.09	1.18
Range of error%	±1.20	±1.00
Calculated *t*-values (2.57)[b]	1.07	0.76
Calculated *F*-test (5.05)[b]	2.47	2.03

[a] A = a + bC, where C is the concentration in μg mL^{-1}.
[b] Values in parentheses are the theoretical values for *t*- and *F*-values at 95% confidence limits and five degrees of freedom.

and 0.58 μg mL^{-1}, using methods A, and B, respectively. Both LOD and LOQ values confirmed the sensitivity of the proposed methods.

3.4.2. Precision

The precision of the methods (within-assay and between-assays) were determined at the AMD concentrations cited in Table 2. The within-assay precision was assessed by analyzing six replicates of each sample as a batch in a single assay run, and the between-assays precision was assessed by analyzing the same sample, as triplicate, in two separate assay runs. The relative standard deviations (RSD) were less than 1.2% (Table 2). This level of precision was adequate for the quality control analysis of AMD.

3.4.3. Specificity and interference

The proposed spectrophotometric methods have the advantages that the measurements are performed in the visible region, away from the UV-absorbing interfering substances that might be co-extracted from AMD containing dosage forms. Regarding the interference of the excipients and additives usually presented in pharmaceutical formulation (sodium lauryl sulfate, magnesium stearate, starch sodium glycolate, lactose spray dried, carboxymethylcellulose PA 102, talc, titanium dioxide, microcrystalline cellulose, hydroxypropylcellulose and pregelanitizated starch), their is no interference indicating the high selectivity of the proposed methods and applicability to use for routine determination in pure and in dosage forms.

3.4.4. Ruggedness and robustness

The ruggedness of the proposed methods was assessed by applying the procedures using two different instruments in two different laboratories at different elapsed time. Results obtained from lab-to-lab and day-to-day variation was found to be reproducible as RSD did not exceed 1.18%. Robustness of the methods was assessed by evaluating the influence of small variation of experimental variables: concentrations reagent, buffer, temperature and reaction time, on the analytical performance of the method. In these experiments, one experimental parameter was changed while the other parameters were kept unchanged, and the recovery percentage was calculated each time. The small variations in any of the variables did not significantly affect the results; recovery percentages were 99.2–100.67, and 99.6–101.4% for methods A and B, respectively. This provided an indication for the reliability of the proposed methods during routine work.

3.5. Applications

3.5.1. Analysis of dosage forms

The obtained satisfactory validation results made the proposed methods suitable for the routine quality control analysis of AMD and its dosage forms pharmaceutical formulations (Amantine, Amantadine, and Viraflu capsules). The results obtained by the proposed methods were statistically compared with those obtained by the official pharmacopoeia method

Table 2 Precision of the proposed methods for analysis of AMD ($n = 6$).

Method	Taken (μg mL^{-1})	Within-assays		Between-assays	
		Mean (μg mL^{-1} ± SD)	RSD%	Mean (μg mL^{-1} ± SD)	RSD%
Fe^{2+}-phen	1.5	1.51 ± 0.49	0.84	1.49 ± 0.76	0.88
	3.0	2.97 ± 0.34	0.68	3.03 ± 0.45	0.65
	4.5	4.48 ± 0.50	0.88	4.51 ± 0.43	0.92
	6.0	6.03 ± 0.47	0.87	5.89 ± 0.59	0.95
	7.5	7.48 ± 0.37	0.74	7.61 ± 0.47	0.78
	9.0	9.89 ± 0.41	1.09	9.11 ± 0.37	1.14
Fe^{2+}-Bipy	4.0	4.06 ± 0.32	0.45	4.05 ± 0.46	0.54
	8.0	8.10 ± 0.33	0.68	7.95 ± 0.54	0.74
	12.0	11.88 ± 0.27	0.59	1.21 ± 0.41	0.63
	16.0	15.90 ± 0.43	0.83	2.39 ± 0.36	0.87
	20.0	20.88 ± 0.45	0.94	3.21 ± 0.31	0.91
	22.0	21.80 ± 0.99	1.18	22.05 ± 0.87	1.05

SD, standard deviations; RSD, relative standard deviations.

(BP, 2007) (based on potentiometric titration, using 0.1 M sodium hydroxide. Each milliliter of 0.1 M sodium hydroxide is equivalent to 18.77 mg of AMD). The obtained mean values of the labeled amounts ranged from 99.80 ± 0.80, and 99.5 ± 0.7%, using A, and B methods, respectively as recorded in Table 3. In the *t*- and *F*-tests, no significant differences were found between the calculated and theoretical values of both the proposed and the reported methods at 95% confidence level (Miller and Miller, 1993). This indicated similar precision and accuracy in the analysis of AMD in its formulations. It is evident from these results that all the proposed methods are applicable to the analysis of AMD in its capsules with comparable analytical performance. However, the critical recommendations of these methods might be based on the experimental conditions and the ultimate sensitivity that determines the amount of specimen required for analysis. For example, the method involving Fe^{2+}-phen is recommended whenever sensitive analysis is required; this because they have very high sensitivity.

Table 3 Determination of AMD in capsules (100 mg/capsule) and spiked plasma by the proposed and official method (BP, 2007).

Parameter	Fe^{2+}-phen	Fe^{2+}-bipy	Official
	Amantine capsule[c]		
Recovery%[a]	100.2 ± 1.2	100.4 ± 1.2	99.6 ± 1.8
±Standard deviation	0.76	0.84	1.20
Number of experiments	6	6	6
Variance	0.81	0.89	1.11
t-test[b]	1.13	0.98	
F-value[b]	2.62	2.43	
	Amantadin capsule[d]		
Recovery%[a]	99.6 ± 0.8	99.4 ± 1.2	99.6 ± 0.7
±Standard deviation	0.88	0.96	0.74
Number of experiments	6	6	6
Variance	0.98	1.08	1.27
t-test[b]	0.76	0.9	
F-value[b]	1.57	2.43	
	Viraflu capsule[e]		
Recovery%[a]	99.8 ± 1.0	99.5 ± 0.7	100 ±1.2
±Standard deviation	0.91	1.11	1.25
Number of experiments	6	6	6
Variance	1.13	1.25	1.42
t-test[b]	0.88	1.17	
F-value[b]	2.12	2.35	
	Spiked plasma pimples		
Mean recovery%[a]	99.5 ± 0.8	99.2 ± 1.0	100.3 ± 1.5
±Standard deviation	1.11	0.92	1.32
Number of experiments	6	6	6
Variance	1.02	0.78	1.23
t-test[b]	1.37	1.19	
F-value[b]	2.88	2.71	

[a] Average values of six determinations were used for the official and the proposed methods, respectively.
[b] Theoretical values for *t* and *F* at 95% confidence limit are 2.57 and 5.05, respectively.
[c] Memphis Pharmaceutical & Chemicals Industries Company, Cairo, Egypt.
[d] Misr Pharmaceutical Industries Company, Cairo, Egypt.
[e] Sigma Pharmaceutical Industries Company, El-Monofeya, Egypt.

3.5.2. Analysis of spiked plasma samples

The high sensitivity attained by the proposed methods allows the determination of AMD, in biological fluids. The method was used to determine the amount of AMD in a healthy male 12 h after an intake of one capsule of AMD, which contains 100 mg AMD. AMD was detected and the results were summarized in Table 3.

4. Conclusions

The redox reaction of AMD using Fe^{3+} has been investigated. The formation of Fe^{2+}-phen and Fe^{2+}-bipy complexes were utilized in the development of simple, accurate, sensitive with good precision and accuracy spectrophotometric methods A and B for the analysis of AMD in pure form as well as in dosage and biological forms. With these methods, one can do the analysis at low cost without losing accuracy. The proposed methods can be used as alternative methods to the official ones for the routine determination of capsules. This encourages their successful use in routine analysis of AMD in quality control laboratories and they involve very simple procedures.

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