Journal of Pharmaceutical and Biomedical Analysis 52 (2010) 203–209

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Investigating the degradation of the sympathomimetic drug phenylephrine by electrospray ionisation-mass spectrometry

Hagen Trommer*, Klaus Raith, Reinhard H.H. Neubert

Martin-Luther-University Halle-Wittenberg, School of Pharmacy, Institute of Pharmaceutics and Biopharmaceutics, Wolfgang-Langenbeck-Straße 4, D-06120 Halle (Saale), Germany

ARTICLE INFO

Article history:
Received 18 August 2009
Received in revised form 5 January 2010
Accepted 8 January 2010
Available online 20 January 2010

Keywords:
Phenylephrine
Stability
Degradation
Electrospray ionisation-mass spectrometry
Fragmentation

ABSTRACT

The frequently used sympathomimetic drug phenylephrine has been studied by electrospray ionisation-mass spectrometry. The stability of the adrenoceptor agonist was examined by investigations of the pharmaceutically used salts phenylephrine hydrochloride and phenylephrine bitartrate. Photostability has been studied by use of an irradiation equipment emitting a solar radiation spectrum. The experiments were carried out by analysis of aqueous drug solutions before and after irradiation treatment. The phenylephrine derivative with unsaturated side chain originating from the drug by loss of one water molecule has been detected as the major degradation product of both phenylephrine salts the hydrochloride and the bitartrate. Further degradation and oxidation products were detectable already in the full scan mode demonstrating a low stability of the drug. Tandem mass spectrometry and multiple stage mass spectrometry experiments enabled the establishment of fragmentation schemes of both salts for the first time. Irradiation treatment indicated that phenylephrine bitartrate is more prone to degradation than the hydrochloride because of an additional decomposition sensitivity of the tartaric acid counter ion. An interaction between phenylephrine and its counter ion degradation products via a nucleophilic addition mechanism is suggested to be the explanation for the detected ion signals after irradiation treatment of phenylephrine bitartrate.

1. Introduction

Phenylephrine belongs to the group of adrenoceptor agonistic drugs with predominantly α_1 sympathomimetic properties. It has got negligible action on α_2 receptors and a low β receptor activity [1]. Phenylephrine is a synthetic compound with almost exclusively direct sympathomimetic action and relatively little indirect effects via the noradrenaline (norepinephrine) release pathway [2]. It is widely used as a decongestant either as an oral medicine or locally as a mucosa decongestant for unspecific and allergic conjunctivitis, sinusitis and nasopharyngitis. Furthermore, the drug is part of some antihaemorrhoidal ointments and is often applied as a mydriatic in ophthalmology to facilitate retina visualisation [3]. When utilized systemically phenylephrine increases blood pressure which explains its therapeutic use as a vasopressor for patients with hypotension. Since hypertension is the primary side effect of phenylephrine the drug should be avoided for congestion treatment of hypertension patients [4].

Chemically phenylephrine is 3-(1-hydroxy-2-methylaminoethyl) phenol. Synonyms are neosynephrine, m-synephrine, neooxedrine, adrianol and others. Compared to its physiologically occurring counterparts adrenaline (epinephrine) and noradrenaline (norepinephrine) it is not hydroxylated at position four of the aromatic ring [5]. Therefore it is more lipophilic and also active after oral administration despite a systemic bioavailability of only around 40% [6,7]. Phenylephrine is the only α sympathomimetic with phenyl-2-amino-ethanol basic structure which is therapeutically used as the pure (R)-(−) enantiomer and not as a racemic mixture [5].

Recently the drug became more interesting again. The Combat Methamphetamine Epidemic Act of 2005 imposed severe restrictions on the sale of pseudoephedrine containing drugs in the USA [8]. Pseudoephedrine is used as a decongestant as well but in contrast to phenylephrine it is more lipophilic, has a central stimulating effect and an abuse potential is ascribed to the substance. The act allows the sales of pseudoephedrine containing medicines only from locked cabinets or behind the counter after presentation of photo identification of the purchaser and further restrictions as a means of controlling the illicit production of methamphetamine [9]. Since the withdrawal of the decongestant phenylpropanolamine in a lot of countries due to abuse concerns and possible links to cerebrovascular stroke, phenylephrine

* Corresponding author at: Bernhard-Kellermann-Str. 16, D-04279 Leipzig, Germany. Tel.: +49 341 330 320 2; fax: +49 341 330 320 2.
E-mail address: hagen.trommer@pharmazie.uni-halle.de (H. Trommer).

0731-7085/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2010.01.024

is almost the only systemic nasal decongestant in common use worldwide now. Phenylephrine has been increasingly marketed as a substitute for pseudoephedrine. A lot of drug products have been reformulated using phenylephrine instead of pseudoephedrine to avoid the restrictions on sale [9,10]. Simultaneously a controversial discussion on the efficacy of phenylephrine and its ability to act as a substitute on a par with pseudoephedrine began resulting from a lack of up to date clinical trials for phenylephrine [9–14].

Fig. 1 shows the chemical structures of the phenylephrine base, its salts mainly used pharmaceutically and the most important related natural and synthetic compounds.

Another consequence of the Combat Methamphetamine Epidemic Act was the approval of phenylephrine bitartrate (phenylephrine hydrogentartrate) as an active ingredient in OTC cough and cold products in effervescent dosage forms by the FDA in August 2006 additionally to phenylephrine hydrochloride [15]. Possibly phenylephrine bitartrate is regarded as a more stable salt compared to the hydrochloride. There exist many investigations reporting a low stability of the hydrochloride salt in aqueous solution on one hand and an increase of the hydrochloride degradation induced by interaction with other actives in combination products on the other hand [16].

Astonishingly, a study establishing an exact degradation mechanism of the molecule could not be found despite the multiplicity of examinations on the stability of phenylephrine and phenylephrine containing drugs carried out over the last five decades [17–21].

Therefore, in this article the stability properties of the pharmaceutically used salts phenylephrine hydrochloride and phenylephrine tartrate are studied.

The fragmentation of phenylephrine and its degradation caused by UV-light were studied to our knowledge for the first time at a molecular level using electrospray ionisation-mass spectrometry (ESI-MS). ESI as a soft ionisation method enabled the analysis of phenylephrine and its degradation products without artificial fragmentation after UV exposure. However, structural elucidation was possible using the capabilities of an ion trap mass analyser [22], namely tandem mass spectrometry (MS/MS) and multiple stage mass spectrometry (MS^n) analysis [23,24].

This experimental setting is in line with the recommendations of the ICH guidelines on stability testing for new active substances where forced degradation studies with the drug substance and the identification of potential degradation products and pathways are required as a base data package before subsequent steps can follow (e.g., focused method development, drug product scrutinies, etc.) [25–27].

The aims of the present study can be summarised as follows: (A) mass spectrometric fragmentation experiments of phenylephrine hydrochloride and phenylephrine bitartrate to allow the establishment of fragmentation schemes in the positive and the negative ion mode, (B) studies on the photostability of the drug salts after irradiation treatment by an equipment emitting a solar radiation spectrum, and (C) comparative stability assessment of both pharmaceutically used phenylephrine salts.

2. Materials and methods

2.1. Materials

Phenylephrine hydrochloride and phenylephrine bitartrate were obtained from Boehringer Ingelheim Fine Chemicals (Ingelheim, Germany) in pharmacopeia defined grade. Phenylephrine hydrochloride complied with the specifications of USP, Pharm Eur, JP and IP. Phenylephrine bitartrate has been certified to meet the specification of the USP monograph. Methanol of gradient grade was purchased from Merck (Darmstadt, Germany).

2.2. Sample preparation

For the experiments aqueous solutions of phenylephrine hydrochloride (100 μM) and phenylephrine bitartrate (100 μM) were prepared by use of doubly distilled water.

The sample solutions were freshly prepared immediately prior to irradiation treatment and mass spectrometric investigations respectively.

2.3. UV irradiation

For the irradiation experiments before mass spectrometry an OSRAM Vitalux 300 W equipment (OSRAM, Augsburg, Germany) emitting a solar radiation spectrum has been used. The distance between the bulb and the sample was 500 mm. Prior to irradiation, the samples (5.0 ml) were transferred to open glass dishes of 55 mm diameter. Thereby, the optical pathlength was 2.1 mm and a homogeneous exposure was assumed in spite of light scattering. All samples were irradiated for 120 min.

2.4. Mass spectrometry

The mass spectrometric analysis was carried out using a Finnigan LCQ ion trap mass spectrometer with ESI interface and integrated syringe pump (Thermo Finnigan, San Jose, CA, USA).

Electrospray ionisation-mass spectrometry was performed in the negative and positive ion mode respectively. After dilution by 1:5 the aqueous samples were mixed with methanol in the ratio 1:1 to guarantee a stable electrospray. The samples were infused via a syringe pump (10 μl/min). Tandem MS and MS^n experiments were used to obtain structural information. The ion optics of the LCQ mass spectrometer were tuned to the drug peaks to allow recordings in the best resolution mode at maximum intensity. The conditions and instrument settings which were implemented for the experiments were as follows: ESI source voltage 4.02–4.08 V; capillary temperature 215–225 °C; capillary voltage ±17.0–17.5 V; octapole 1 offset voltage ±4.0–5.0 V; octapole 2 offset voltage ±7.0–8.0 V; interoctapole lens offset voltage ±87.0–89.0 V; source fragmentation offset voltage 0.0 V. For MS/MS experiments isolation width adjustments between 2 and 3 mass units were applied. The relative collision energy utilized for MS/MS and MS^n ion trap experiments varied from 5% to 40% which corresponds to mass analyzer fragmentation voltages between 0.25 V and 2.0 V.

All mass spectrometric operations were carried out four times resulting in similar spectra.

3. Results and discussion

3.1. Phenylephrine hydrochloride

Fig. 2 shows the positive ion mode mass spectrum of phenylephrine hydrochloride. The protonated molecule ion $[M+H]^+$ of the phenylephrine base was detected at $m/z = 168$. Surprisingly, another ion signal at $m/z = 150$ has been detected as well in the full scan mode without attendance of fragmentation energy as used for the MS/MS experiments. The signal was assigned to the dehydrated phenylephrine illustrated also in Fig. 2. Besides natural instability of the drug molecule ESI in-source fragmentation has to be considered to account for this observation as well. However, no additional source fragmentation collision energy has been applied to facilitate this process.

Fig. 3 shows the positive ion mode tandem MS (MS/MS) and multiple MS mass spectra of phenylephrine hydrochloride. To our

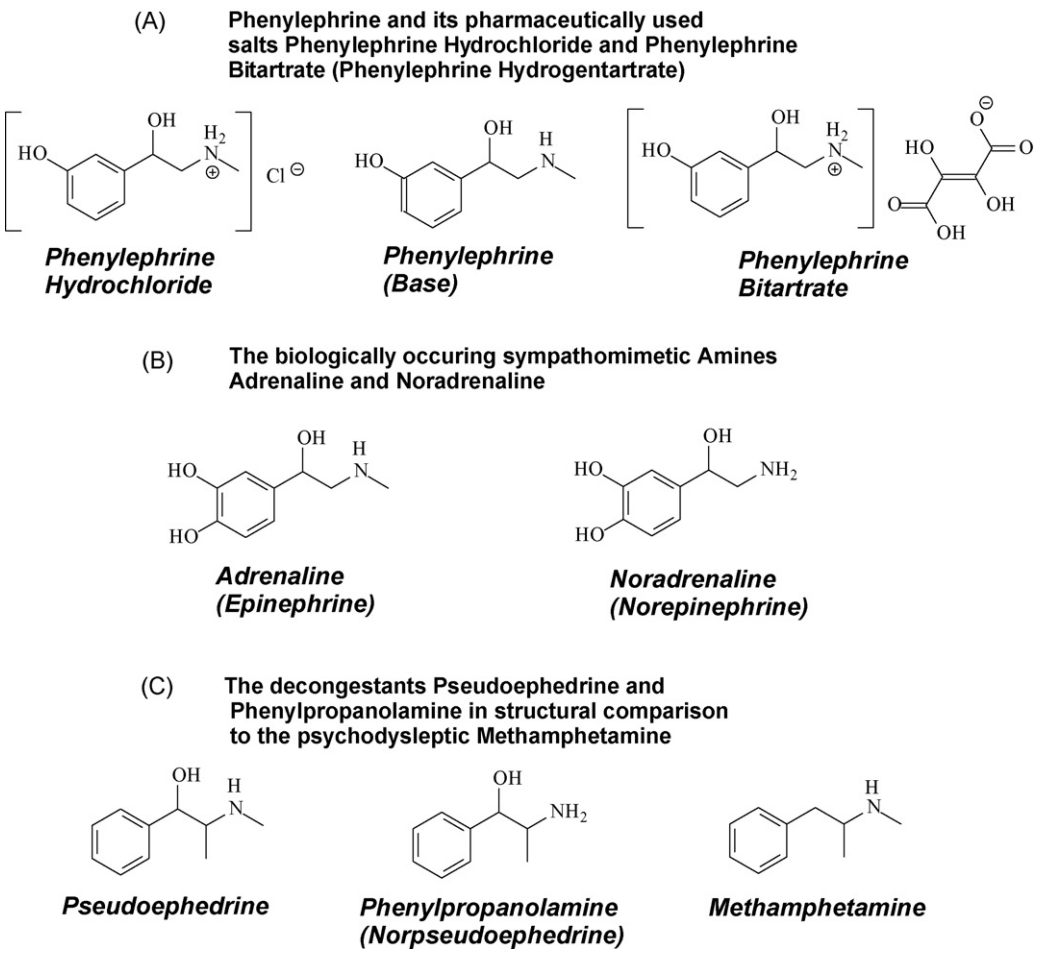

Fig. 1. Chemical structures of phenylephrine and related natural and synthetic compounds.

knowledge for the very first time ESI tandem MS and ESI-MS^n fragmentation experiments of the sympathomimetic drug phenylephrine were conducted for structural elucidation.

Fig. 3(A) shows the tandem mass spectrum of $m/z = 168$. The $m/z = 150$ ion as the dehydrated phenylephrine was detected as the only fragment in this experiment. Further fragmentation of the $m/z = 150$ ion in a MS^3 experiment led to several peaks at $m/z = 135$, $m/z = 132$, $m/z = 121$, $m/z = 119$, $m/z = 109$ and $m/z = 91$ (Fig. 3(B)). The MS^4 experiment of the main peak detected at $m/z = 119$ gave rise to an ion signal at $m/z = 91$ (Fig. 3(C)).

Fig. 4 shows the full scan mass spectrum of phenylephrine hydrochloride in the negative ion mode. Fragmentation experiments were not successful in this case. This can be explained with the elimination of chlorine by charge entrainment after MS/MS fragmentation. The charged chlorine owns a too low m/z ratio to be detected under these conditions and the neutral rests are invisible because of the missing charges.

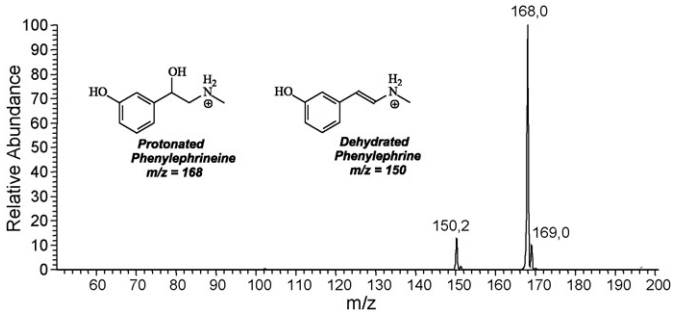

Fig. 2. Positive ion mode ESI mass spectrum of phenylephrine hydrochloride.

Fig. 5 illustrates the results of the structural assignments in the negative and in the positive ion mode.

Interestingly, in the positive ion mode only one ion ($m/z = 132$) has been generated by retaining the secondary amine function after the fragmentation experiments. This is in good accordance with the early observations of El-Shibini et al. [18]. The disappearance of the secondary side chain amino group has been used to investigate the rate of phenylephrine degradation in aqueous solution kinetically. The results indicated that the decomposition follows a first order kinetic equation with a pH-dependent reaction rate.

The deprotonated molecule ion $[M-H]^-$ was detected at $m/z = 166$ in the neagative ion mode. Furthermore several chlorine ion adducts were measured showing the typical isotope pattern of chlorine 35 and chlorine 37 with its proportion of approximately 3:1. The presence of one or two chlorine ions could be revealed easily by assessment of the ion intensity.

The ions at $m/z = 196/198$ were assigned to the phenylephrine derivative ions deriving from oxidative cyclisation. The indole derivative formation can be regarded as an analogue of the adrenochrome reaction of the pyrocatechol adrenaline [28] and explains that the intensity proportion of $m/z = 196/198$ does not match to the chlorine isotope pattern. This is because the $m/z = 198$ is generated by two ionic species. Surprisingly, this oxidation product has been detected in the full scan mode under normal ESI conditions without further energy supply. This cyclic conversion of phenylephrine into 5-hydroxy-N-methyl-indoxyl under oxidative

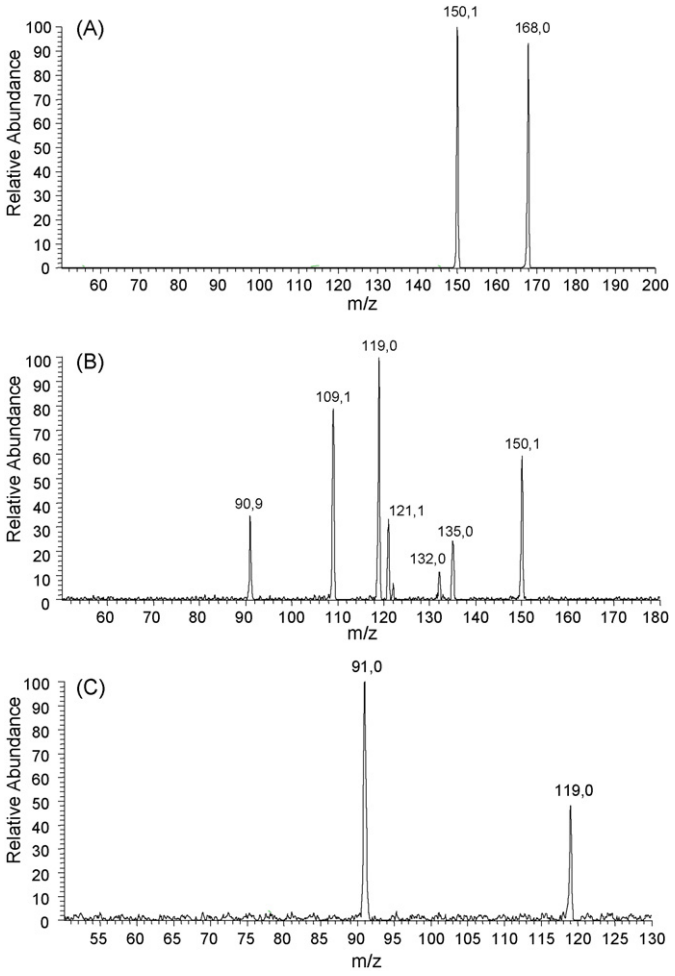

Fig. 3. Positive ion mode ESI mass spectra of phenylephrine hydrochloride. (A) Tandem mass spectrum of $m/z = 168$. (B) MS^3 spectrum of $m/z = 168$, $m/z = 150$. (C) MS^4 spectrum of $m/z = 168$, $m/z = 150$, $m/z = 119$.

conditions has been proposed by El-Shibini et al. as well without proofing this suggestion by decomposition product identification [18]. In contrast Millard et al. [29] did not detect indols by their GC–MS investigations. The mass spectrometric ion signals following phenylephrine degradation experiments of this group were assigned to isoquinoline derivatives as oxidation products. As a reaction mechanism a Pictet–Spengler reaction was supposed.

The detection of different degradation products in the positive and in the negative ion mode already in the full scan mass spectrometry mode by use of the soft ionisation technique of electrospray in our experiments suggests that phenylephrine hydrochloride is not a very stable drug substance and should be handled with caution when formulated to drug products.

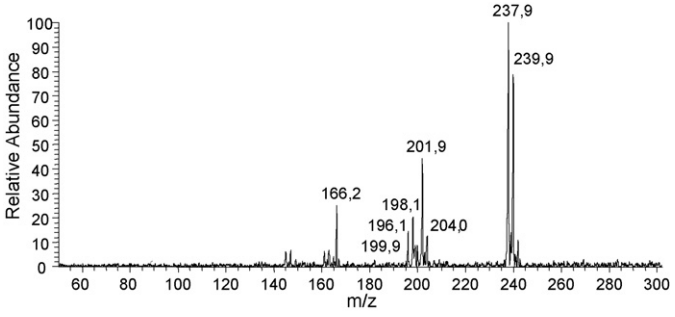

Fig. 4. Negative ion mode ESI mass spectrum of phenylephrine hydrochloride.

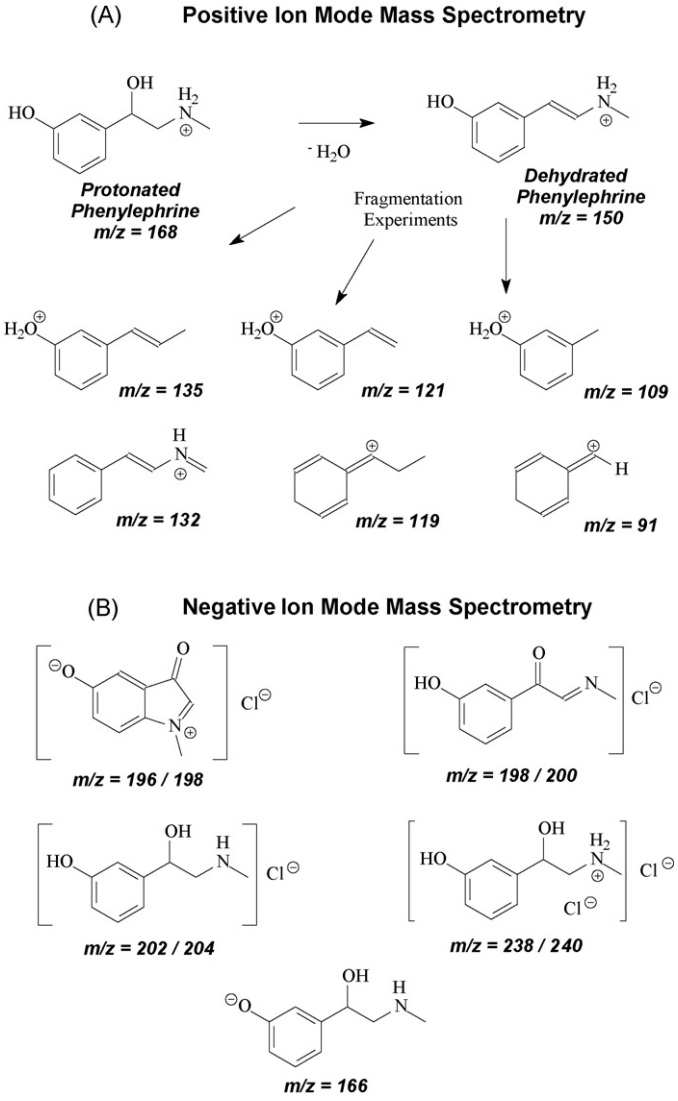

Fig. 5. Scheme of the phenylephrine hydrochloride decomposition after multiple stage MS experiments in the positive ion mode and signal assignment in the negative ion mode.

This outcome is in good accordance with the research results of other groups obtained by colour analysis [30], by UV absorbance measurements after cationic exchange resin separation [31], by GC–MS following trimethylsilyl derivatization [29], by HPLC [32] and by LC/MS [33].

It has been proved by our experiments for the first time via signal assignment to the exact degradation product structures.

In contrast, recently Kiser et al. were able to show that phenylephrine hydrochloride is stable for at least 30 days when stored in propylene syringes at −20 °C, 3–5 °C and 23–25 °C when diluted to 100 μg/mL in 0.9% sodium chloride injection [34]. Aim of this study was to provide a protocol that allows the preparation of the syringes in advance and their storage over a specific period.

3.2. Phenylephrine bitartrate

The mass spectrometric experiments with phenylephrine bitartrate in the positive ion mode gave identical results as measured by use of the hydrochloride.

The spectra obtained in the negative ion mode are demonstrated in Fig. 6.

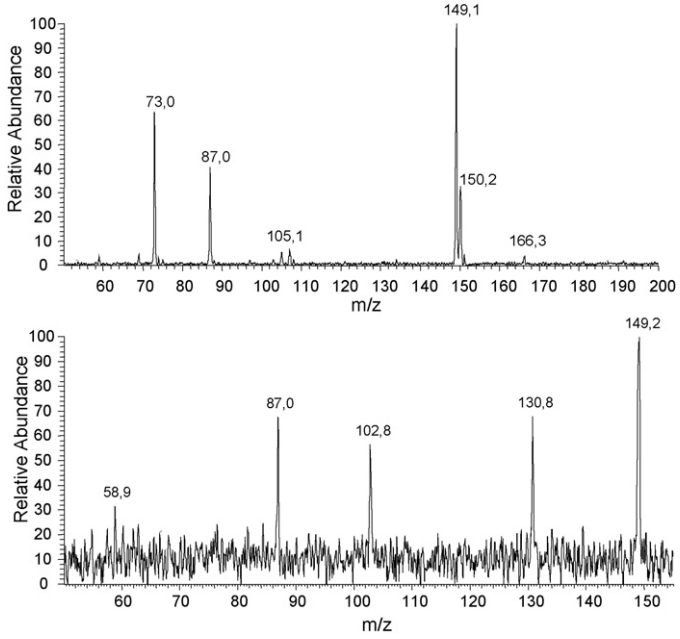

Fig. 6. Negative ion mode ESI mass spectrum of phenylephrine bitartrate. (A) Full scan mass spectrum. (B) Tandem mass spectrum of $m/z = 149$.

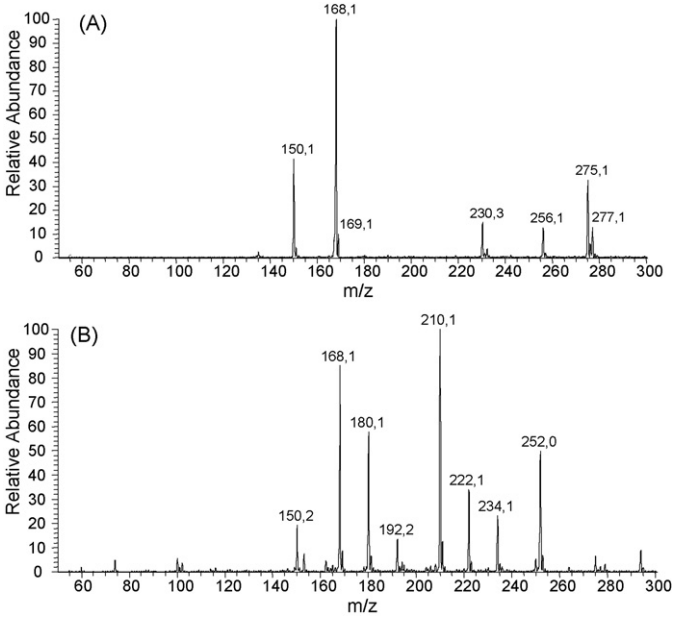

Fig. 8. Positive ion mode ESI full scan mass spectra after 120 min irradiation. (A) Phenylephrine hydrochloride. (B) Phenylephrine bitartrate.

Fig. 6(A) shows the low intensity of the deprotonated molecule ion $[M-H]^-$ at $m/z = 166$. The dehydrated phenylephrine at $m/z = 150$ has been detected again. The ions with the most intense peaks were recorded at $m/z = 149$, $m/z = 87$ and $m/z = 73$. Additionally a weaker signal at $m/z = 105$ has been recorded.

Further fragmentation of the base peak at $m/z = 149$ resulted in $m/z = 87$ as well and new ion signals at $m/z = 131$, $m/z = 103$ and $m/z = 59$.

All the detected ions were assigned to structures as demonstrated in Fig. 7.

The species measured in the negative ion mode are related to the tartaric acid anion which is present as a counter ion in phenylephrine bitartrate. Surprisingly, the tartaric acid moiety was also found to be a source of instability. Again, already in the full scan mode decomposition products were analysed resulting from carbonic acid degradation this time.

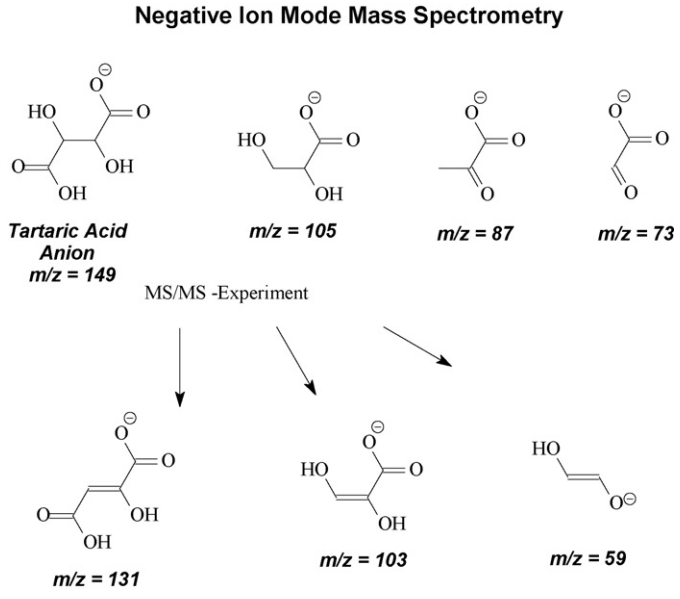

Fig. 7. Scheme of the phenylephrine bitartrate/tartaric acid decomposition after the tandem MS experiment in the negative ion mode.

3.3. Irradiation experiments

Fig. 8 represents the results of the irradiation studies with both molecules phenylephrine hydrochloride (Fig. 8(A)) and phenylephrine bitatrate (8(B)). These experiments were carried out as photostability tests simulating natural drug substance aging by use of forced conditions.

It can be gathered from the spectra that irradiation treatment induced the formation of different secondary products at both salts. Irradiation of phenylephrine hydrochloride gave only four additional peaks ($m/z = 230$, $m/z = 256$, $m/z = 275$, $m/z = 277$) with lower intensity than the signals already known from the experiments without irradiation (protonated molecule ion at $m/z = 168$ and dehydrated phenylephrine at $m/z = 150$).

Luduena et al. had reported the formation of adrenaline after UV irradiation experiments and subsequent photofluorometic determination [35]. The group used bioassays for the experiments where an increase in biological activity of the irradiated samples has been measured. Adrenaline is readily ionised in ESI and should appear at $m/z = 185$. However, under the conditions used in this study, no adrenaline was detected. Chafetz and Chow reported an adrenaline content of about 2% of the initial content which they were able to detect by HPLC and gas chromatography after irradiating phenylephrine solutions for several hours by a shortwave UV source [36]. This photochemical hydroxylation has been stated by the authors as an exotic reaction in vitro because oxidative attack at the electron rich four position of the ring system is quite unlikely to occur.

The irradiation of phenylephrine bitartrate resulted in six new ion signals ($m/z = 180$, $m/z = 192$, $m/z = 210$, $m/z = 222$, $m/z = 234$, $m/z = 252$) and a novel base peak at $m/z = 210$.

The ion signal at $m/z = 180$ can be assigned to several structures. The formation of isomeric isoquinolines as a result of oxidative side chain alteration and subsequent ring closure has been suggested by Millard et al. [29]. The structures of these tetrahydroisoquinoline derivatives are illustrated in Fig. 9 for completeness. To our minds the open chain phenylephrine derivative structure at $m/z = 180$ is more probable. Interestingly, only phenylephrine bitartrate shows

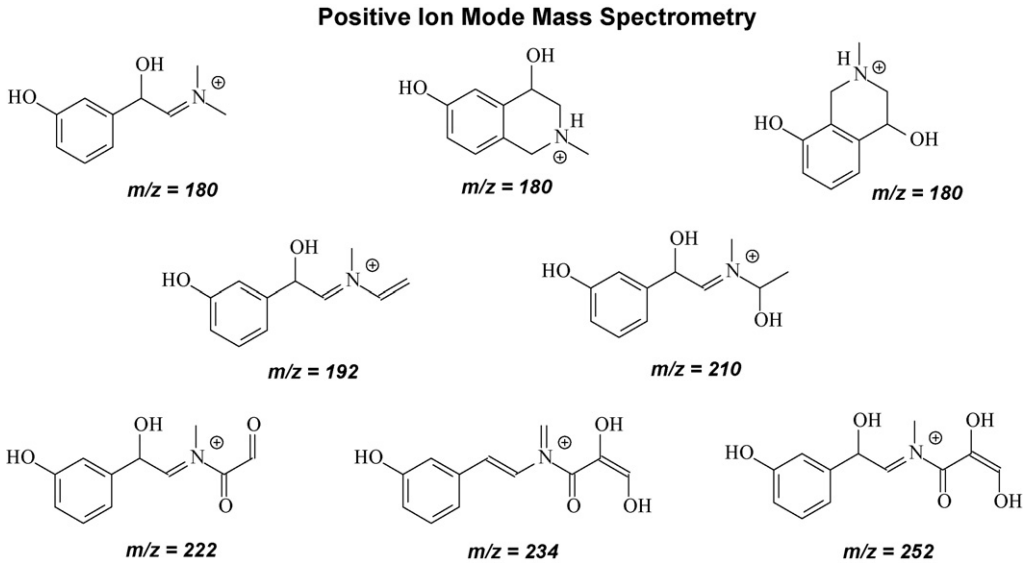

Fig. 9. Scheme with suggested structures of the phenylephrine bitartrate derived ions after irradiation in the positive ion mode.

the ion signal at $m/z = 180$ after irradiation treatment. Millard et al. also suggested 3-hydroxybenzaldehyde as a degradation product in their proposed oxidation pathway for phenylephrine in aqueous solution [29]. This ion should appear at $m/z = 123$ and was not detected under the conditions used in this study.

Recently Marín et al. have investigated different pharmaceutical formulations against the common cold containing acetaminophen, phenylephrine hydrochloride and chlorpheniramine maleate [37]. As a result a new compound was isolated and identified for the first time as a product formed from the interaction between phenylephrine and maleate. Based on this findings further investigations have been carried out by Wong et al. including the synthesis of the possible interaction products and their MS and NMR characterization [38]. It was concluded that the compound observed during the short and long term stability studies of the pharmaceutical cold preparations is a "Michael addition" product between phenylephrine and maleic acid.

According to these findings and according to the measured instability of the tartaric acid ion as illustrated above, Fig. 9 shows structural suggestions for the ion signals detected after phenylephrine bitartrate irradiation.

The rationale for this hypothesis is the interaction of phenylephrine with its own counter ion tartaric acid under the experimental conditions of the study. The nucleophilic addition of the secondary amine phenylephrine to the carbonyl compounds (tartaric acid decomposition products) is supposed to be the reaction mechanism. Vinylogic carbonyls as tartaric acid degradation derivatives would be able to react via a "Michael addition" as a nucleophilic addition special case in analogy to the findings of Wong et al. for maleic acid. Phenylephrine acts as a typical neutral nucleophilic agent at any rate.

These results show that the pharmaceutically used phenylephrine salts phenylephrine hydrochloride and phenylephrine bitartrate are prone to degradation and therefore should be handled carefully during pharmaceutical processing.

Maybe these drawbacks of the phenylephrine containing drugs could be overcome by use of the sympathomimetic in form of more stable salts. Besides the hydrochloride and the bitartrate the use of phenylephrine tannate and phenylephrine pivalate is described in the literature [39,40]. Generally, the absence of carbon double bonds in the counter ion of the salts should avoid interactions via the nucleophilic addition pathway as described in this work. Further efforts to synthesise tailor made phenylephrine derivatives with optimised properties such as increased bioavailability and enhanced stability led to the development of phenylephrine oxazolidines [41]. Another approach was the synthesis and characterisation of bioreversible phenylephrone derivatives [42]. The preparation of a "caged" phenylephrine as a product of selective derivatization on the amine function was an approach to probe the mechanism of α receptor mediated vasoconstriction in isolated adult rat mesenteric arterioles [43].

Due to the rapid developments in the area of mass spectrometry mainly in the last three decades and the resulting versatility of the modern equipment MS has become a preferred tool also in doping control laboratories allowing a fast analysis of controlled substances [44,45]. Against this background the present study should be of interest additionally for forensic analytical investigations. Even though the production of methamphetamine from phenylephrine is much more difficult compared to the various straightforward reactions for the clandestine manufacturing of methamphetamine from pseudoephedrine, phenylephrine has a certain potential to appear in methamphethamine case samples as well. Considering that it becomes clear that unequivocal identification methods for each of these chemically quite similar molecules are required. This task is much more a challenge when taking into account that there are unique fragmentation products of phenylephrine and methamphetamine but common fragments as well [44]. MS fragmentation analysis based on the initial findings of the present study could be used for this application after development and optimisation of an adequate method.

4. Conclusion

In this study electrospray ionisation-mass spectrometry with ion trap analyser has been applied to investigate the complex matter of the degradation of phenylephrine, a widely used sympathomimetic drug substance. The two pharmaceutical salts used most frequently, namely phenylephrine hydrochloride and phenylephrine bitartrate, were included into the examinations. It was shown that the dehydrated phenylephrine derivative is the major degradation product of both salts under the test conditions employed. The detection of this species was possible without any fragmentation energy in the positive ion full scan mode.

To elucidate the mechanism of phenylephrine hydrochloride decomposition at a molecular level, fragmentation experiments were conducted. In the positive ion mode MS/MS, MS^3 and MS^4 spectra were recorded allowing structural signal assignments for the first time. The negative ion mode mass spectrum revealed several chlorine ion adducts and an ionic species which is suggested to be an indole derivative resulting from oxidative cyclisation.

Fragmentation experiments of phenylephrine bitartrate in the positive ion mode led to the same results as observed for the hydrochloride. The investigations in the negative ion mode revealed the instability of the phenylephrine bitartrate counter ion tartaric acid. Several decomposition products have been identified already in the full scan mode. More degradation was observed after specific fragmentation in the MS/MS experiment. Structural assignments to all the detected peaks succeeded in this case as well.

Photostability studies carried out after irradiation treatment suggest that phenylephrine bitartrate is more prone to degradation than the hydrochloride. This is ascribed to an instability of both parts of the salt – the protonated phenylephrine as well as the anionic counter ion. Considering the results of other research groups published on this topic recently the ionic structures detected after phenylephrine bitartrate irradiation were suggested to be products of an interaction between phenylephrine and its own counter ion degradation derivatives via a nucleophilic addition mechanism.

The results indicate that phenylephrine salts are molecules which should be handled with special care during pharmaceutical processing to avoid decomposition and interactions. The quantification of the degradation products detected in this study should be carried out by liquid chromatography–mass spectrometry (LC/MS) accompanied by NMR identification and characterisation of these products. This will generate further data and options allowing a more detailed stability prognosis and predictions in a quantitative manner as well.

References

[1] H. Akita, H. Akamatsu, K. Matsunaga, Allergic contact dermatitis due to phenylephrine hydrochloride, with an unusual patch test reaction, Contact Dermatitis 49 (2003) 232–235.
[2] M.J. Miller-Meeks, T.A. Farrell, P.M. Munden, J.C. Folk, C. Rao, R.D. Schoenwald, Phenylephrine prodrug. Report of clinical trials, Ophthalmology 98 (1991) 222–226.
[3] V.R. Goskonda, H. Ghandehari, I.K. Reddy, Novel site-specific chemical delivery system as a potential mydriatic agent: formation of phenylephrine in the iris-ciliary body from phenylephrone chemical delivery systems, J. Pharm. Sci. 90 (2001) 12–22.
[4] B.B. Hoffman, Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists, in: J.G. Hardman, L.E. Limbrid, A.G. Gilman (Eds.), Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 10th ed., McGraw-Hill, Med. Pub. Div., New York, 2001, pp. 215–268.
[5] D. Steinhilber, M. Schubert-Zsilavecz, H.J. Roth, Medizinische Chemie. Targets und Arzneistoffe, DAV, Stuttgart, 2005.
[6] I. Kanfer, R. Dowse, V. Vuma, Pharmacokinetics of oral decongestants, Pharmacotherapy 13 (1993) 116S–128S.
[7] J.H. Hengstmann, J. Goronzym, Pharmacokinetics of 3H-phenylephrine in man, Eur. J. Clin. Pharmacol. 21 (1982) 335–341.
[8] Drug Enforcement Administration, General Information Regarding the Combat Methamphetamine Epidemic Act of 2005 (Title VII of Public Law 109–177), 2006 http://www.deadiversion.usdoj.gov/meth/cma2005_general_info.pdf.
[9] R. Eccles, Substitution of phenylephrine for pseudoephedrine as a nasal decongeststant. An illogical way to control methamphetamine abuse, Br. J. Clin. Pharmacol. 63 (2007) 10–14.
[10] K. Hillenmeyer, All stuffed up. Reformulated cold medicines might not be able to do the job, Herald Tribune, 30.01.2007.
[11] L. Hendeles, R.C. Hatton, Oral phenylephrine: an ineffective replacement for pseudoephedrine? Letters to the editor, J. Allergy Clin. Immunol. 118 (2006) 279–280.
[12] R. Eccles, Efficacy of phenylephrine. Letter to the editor, Br. J. Clin. Pharmacol. 64 (2007) 557.
[13] P.J. Desjardins, R.G. Berlin, Efficacy of phenylephrine. Letter to the editors, Br. J. Clin. Pharmacol. 64 (2007) 555–556.
[14] K. Traynor, FDA advisers want more data about phenylephrine, Am. J. Health Syst. Pharm. 65 (2008) 193–194.
[15] FDA, Nasal Decongestant Drug Products: Phenylephrine Bitartrate. Final Rule: Adds effervescent tablet as GRASE dosage form, 2006 (71FR43358) http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-12265.pdf.
[16] A.E. Troup, H. Mitchner, Degradation of phenylephrine hydrochloride in tablet formulations containing aspirin, J. Pharm. Sci. 53 (1964) 375–379.
[17] C.A. Gaglia, Phenylephrine hydrochloride, in: K. Florey (Ed.), Analytical Profiles of Drug Substances, vol. 3, Academic Press, New York, 1974, pp. 483–512.
[18] H.A.M. El-Shibini, N.A. Daabis, M.M. Motawi, The stability of phenylephrine. I. The rate of degradation of the amino group, Arzneimittelforschung 19 (1969) 676–678.
[19] H.A.M. El-Shibini, N.A. Daabis, M.M. Motawi, The stability of phenylephrine. II. The discolouration reaction and the influence of some ions on the rate of degradation of the drug, Arzneimittelforschung 19 (1969) 828–831.
[20] H.A.M. El-Shibini, N.A. Daabis, M.M. Motawi, The stability of phenylephrine. III. The racemisation reaction, Arzneimittelforschung 19 (1969) 1613–1614.
[21] V. Vuma, I. Kanfer, High-performance liquid chromatographic determination of phenylephrine in human serum with coulometric detection, J. Chromatogr. B: Biomed. Appl. 678 (1996) 245–252.
[22] D.I. Papac, Z. Shahrokh, Mass spectrometry innovations in drug discovery and development, Pharm. Res. 18 (2001) 131–145.
[23] M.J. Galmier, B. Bouchon, J.C. Madelmont, F. Mercier, F. Pilotaz, C. Lartigue, Identification of degradation products of diclofenac by electrospray ion trap mass spectrometry, J. Pharm. Biomed. Anal. 38 (2005) 790–796.
[24] G. Bedse, V. Kumar, S. Singh, Study of forced decomposition behavior of lamivudine using LC, LC–MS/TOF and $MS^{(n)}$, J. Pharm. Biomed. Anal. 49 (2009) 55–63.
[25] International Conference on Harmonisation, Q1A(R2), Stability Testing of New Drug Substances and Products, November 2003.
[26] International Conference on Harmonisation, Q1B, Photostability Testing of New Active Substances and Medicinal Products, May 1997.
[27] S.W. Baertschi, Analytical methodologies for discovering and profiling degradation-related impurities, Trends Anal. Chem. 25 (2006) 758–767.
[28] J. Brustugun, S. Kristensen, H.H. Tønnesen, Photostability of epinephrine – the influence of bisulfite and degradation products, Pharmazie 59 (2004) 457–463.
[29] B.J. Millard, D.J. Priaulx, E. Shotton, The stability of aqueous solutions of phenylephrine at elevated temperatures: identification of the decomposition products, J. Pharm. Pharmacol. 25 (Suppl.) (1973) 24P–31P.
[30] G.B. West, T.D. Whittet, A note on the stability of solutions of phenylephrine, J. Pharm. Pharmacol. 12 (Suppl.) (1960) 113–115.
[31] E. Shotton, D.J. Priaulx, An assay for phenylephrine applicable to stability studies, J. Pharm. Pharmacol. 26 (1974) 197–200.
[32] G.W. Schieffer, D.E. Hughes, Simultaneous stability-indicating determination of phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin in dosage forms by reversed-phase paired-ion high-performance liquid chromatography, J. Pharm. Sci. 72 (1983) 55–59.
[33] A. Marín, C. Barbas, LC/MS for the degradation profiling of cough–cold products under forced conditions, J. Pharm. Biomed. Anal. 35 (2004) 1035–1045.
[34] T.H. Kiser, A.R. Oldland, D.N. Fish, Stability of phenylephrine hydrochloride injection in polypropylene syringes, Am. J. Health Syst. Pharm. 64 (2007) 1092–1095.
[35] F.P. Luduena, A.L. Snyder, A.M. Lands, Effect of ultra-violet irradiation of phenylephrine solutions, J. Pharm. Pharmacol. 15 (1963) 538–543.
[36] L. Chafetz, L.H. Chow, Photochemical hydroxylation of phenylephrine to epinephrine (adrenaline), J. Pharm. Biomed. Anal. 6 (1988) 511–514.
[37] A. Marín, A. Espada, P. Vidal, C. Barbas, Major degradation product identified in several pharmaceutical formulations against the common cold, Anal. Chem. 77 (2005) 471–477.
[38] J. Wong, L. Wiseman, S. Al-Mamoon, T. Cooper, L.K. Zhang, T.M. Chan, Major degradation product identified in several pharmaceutical formulations against the common cold, Anal. Chem. 78 (2006) 7891–7895.
[39] J.M. Weiler, M. Gellhaus, A. Donnelly, K. Weiler, Randomized, double-blind, parallel groups, placebo-controlled study of efficacy and safety of Rynatan in the treatment of allergic rhinitis using an acute model, Ann. Allergy 64 (1990) 63–67.
[40] J.S. Mindel, S.T. Shaikewitz, S.M. Podos, Is phenylephrine pivalate a prodrug? Arch. Ophthalmol. 98 (1980) 2220–2223.
[41] Y. Qiu, J.K. Guillory, R.D. Schoenwald, Formulation, in vitro dissolution, and ocular bioavailability of high- and low-melting phenylephrine oxazolidines, Pharm. Res. 10 (1993) 1627–1631.
[42] V.R. Goskonda, M.A. Khan, N.S. Bodor, I.K. Reddy, Chemical delivery systems: evaluation of physicochemical properties and enzymatic stability of phenylephrone derivatives, Pharm. Develop. Technol. 4 (1999) 189–198.
[43] S. Muralidharan, G.M. Maher, W.A. Boyle, J.M. Nerbonne, "Caged" phenylephrine: development and application to probe the mechanism of alpha-receptor-mediated vasoconstriction, Proc. Natl. Acad. Sci. U.S.A. 90 (1993) 5199–5203.
[44] M. Thevis, W. Schänzer, Mass spectrometry in sports drug testing: structure characterization and analytical assays, Mass Spectrom. Rev. 26 (2007) 79–107.
[45] S.E. Rodriguez-Cruz, Rapid analysis of controlled substances using desorption electrospray ionization mass spectrometry, Rapid Commun. Mass Spectrom. 20 (2006) 53–60.