ELSEVIER

International Journal of Pharmaceutics 195 (2000) 159–169

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Artefact formation in the determination of residual solvents according to a method of the European Pharmacopeia

C.R. Lee *, C. Nguyen van Dau, A.M Krstulović

Analytical Development Department, Synthélabo Recherche, 5 Rue Georges Bizet, 91160 Longjumeau, France

Received 15 September 1999; accepted 1 November 1999

Abstract

Method 2 of the procedure for the identification and assay of residual solvents, of the European Pharmacopeia 3rd edition 1999 addendum, leads to artefactual formation of *N*-chlorodimethylamine when the hydrochlorides of basic compounds are examined. This is due to degradation of the dissolution solvent *N*,*N*-dimethylformamide under the prescribed conditions. *N*-Chlorodimethylamine has been detected during analysis of several hydrochloride salts of nitrogen bases including drug substances. Artefact formation did not occur consistently with all the compounds examined, but with diltiazem hydrochloride it was observed in the majority of experiments. The discovery that the alkylating reagent *N*,*N*-dimethylaminoethyl chloride (DMC) used in the synthesis of diltiazem gives apparently high yields of *N*-chlorodimethylamine was cause for concern. However, it has been confirmed that production batches of diltiazem hydrochloride contain < 1 ppm of this synthetic intermediate. The formation of *N*-chlorodimethylamine in the presence of the drug substance is probably due to a reaction between dimethylformamide and HCl, that would be released as a result of hydrolysis by residual water of the *O*-acetyl function of diltiazem. In view of these findings, the compendial general method should be reviewed. It may be necessary to adopt a different approach to the drafting of methods for volatile impurities, since most of the operating conditions are in practice specific to the substance being examined.

Keywords: Diltiazem; GC-headspace analysis; Pharmacopeial method

1. Introduction

Official analytical monographs for drug substances usually include a test for volatile impurities (residual solvents according to the terminology of the European Pharmacopeia). Injection methods that have been proposed or adopted for the GC analysis of residual solvents are: direct injection of a solution in a suitable solvent; the purge and trap technique and the static equilibrium headspace technique. Direct injection can be useful in specific cases, but it is unsuitable as a routine compendial method, because the injector and column rapidly become contaminated. The purge and trap technique is relatively complex, and since it has no advantages over static headspace analysis whenever a homogeneous solution of the drug substance can be

* Corresponding author.

0378-5173/00/$ - see front matter
PII: S0378-5173(99)00386-5

obtained, the latter is the most widely used technique. The relatively recent and more convenient technique of solid phase micro extraction (SPME; Supelco) is tending to replace headspace analysis in many areas, but it is unlikely to cover the range of solvent polarities encountered in the present application.

The choice of dissolution solvent and equilibration temperature for static headspace analysis depends on the solubility and other properties of the drug substance, and on the volatile impurities being searched for. Consequently, the selection of a limited set of alternative experimental conditions suitable for a compendial method has proved difficult. The 1999 addendum of the European Pharmacopeia (1999a) describes three standard systems which are to be used whenever possible: water (80°C), *N*,*N*-dimethylformamide (105°C) and 1,3-dimethyl-2-imidazolidinone (80°C).

In this report, we demonstrate that the use of method 2 (dimethylformamide) for the analysis of residual solvents in diltiazem hydrochloride (Fig. 1) leads intermittently to the formation of an artefactual GC peak, identified as *N*-chlorodimethylamine. The peak is not specific to this drug substance, and it is detected with several other hydrochloride salts.

During investigations of this reaction, it was found that considerable amounts of *N*-chlorodimethylamine are formed by reaction with dimethylformamide of a synthetic intermediate of diltiazem, the alkylating agent *N*,*N*-dimethylaminoethyl chloride (DMC; Fig. 2). Because

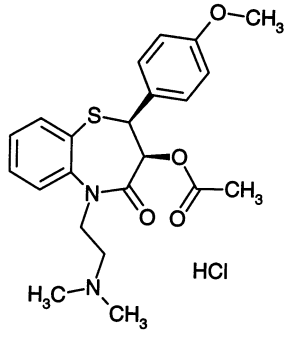

Fig. 1. Structure of diltiazem hydrochloride.

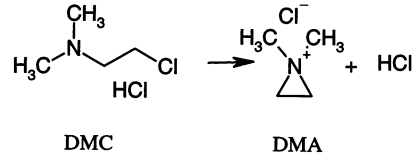

Fig. 2. Formation of *N*,*N*-dimethylaziridinium ion by cyclisation of *N*,*N*-dimethylaminoethyl chloride (DMC).

DMC belongs to a family of notoriously toxic alkylating agents (Golumbic et al., 1946), it was necessary to establish beyond all reasonable doubt that neither this compound nor its cyclisation product the *N*,*N*-dimethylaziridinium ion (DMA; Fig. 2) is present in diltiazem hydrochloride.

2. Experimental

2.1. Materials

Production batches of diltiazem hydrochloride manufactured by Synthélabo were used, together with a few samples obtained from other sources. Deuterated dimethylformamide was purchased from CEA, Saclay, France. *N*-Chloro-*N*,*N*-dimethylamine and *N*-chloro-*N*,*N*-diethylamine were prepared by adding one equivalent of *N*-chlorosuccinimide or sodium hypochlorite to solutions (1 meq/100 ml) of the amines in diethyl ether. The resulting solutions were used directly for GC analysis. Other reagents and solvents were obtained from Aldrich, Fluka or Merck.

2.2. Methods

Stock solutions of diltiazem hydrochloride (200 mg) in dimethylformamide were prepared in 20 ml volumetric flasks. Some solutions were sonicated for 20 min, in order to simulate the conditions used for the analysis of solid dosage forms.

Aliquots (5.0 ml) of the stock solutions were placed in 20 ml glass headspace vials (Perkin Elmer), followed by 1.0 ml dimethylformamide (which could contain standard additions of potential impurities). The vials were immediately crimp-sealed with PTFE-lined silicone rubber septa, and the contents were gently mixed.

Head-space analysis was carried out either manually or by means of an automatic injector. In both cases, the vials were heated at 105 ± 2°C for 45 min.

For manual injections, the vials were not agitated during heating. The pressure was released by piercing the septum with a hypodermic needle, which provided a passage for the needle of a 1-ml gas-tight syringe. The syringe was maintained at ~95°C on a hot-plate. The volume injected was 1.0 ml.

The automatic injector (Hewlett–Packard Model 7694) was fitted with a 1 ml nickel sample loop, and the transfer lines were also of nickel. In some experiments the vials were not agitated; in others, they were agitated at the higher of the two available speeds. The loop and transfer line were maintained at 110°C.

GC/MS was carried out using a Hewlett–Packard 5890 GC coupled directly to a 5989A quadrupole mass spectrometer, with Windows Chemstation software. Two GC columns coated with bonded and crosslinked polyethylene glycol were used during the study: Chrompack CP Wax 52 CB (25 m × 0.32 mm, film thickness 1.5 μm), and Hewlett–Packard Innowax (60 m × 0.32 mm, film thickness 0.5 μm).

The carrier gas (helium) pressure was regulated at 7 psi (48 kPa) for the Chrompack column and 10 psi (69 kPa) for the Hewlett–Packard column. The split/splitless injector was maintained at 140°C, with a split flow of 12 ml/min. The column was operated isothermally at 50°C for 5 min, and then purged at 170°C for 5 min. The temperature of the interface and ion source was 250°C.

The mass spectrometer was operated in electron impact mode, and tuned in order to optimise sensitivity at $m/z < 120$. Acquisions were performed either by scanning from m/z 30 to 200 (1.3 scans/s), or by selected ion recording of m/z 42, 78 and 79 (dwell time 100 ms).

3. Results

3.1. Identification of the artefact formed in the presence of diltiazem

When analysed by headspace method 2 (dimethylformamide as dissolution solvent), diltiazem hydrochloride gave, on random occasions, a GC peak of variable intensity, with a retention time of 1.1–1.4 min on the Chrompack column and 4.75 min on the Hewlett–Packard column. The peak was identified by its mass spectrum (Fig. 3), which matched library spectra of *N*-chlorodimethylamine. A sample of this compound synthesised by a standard method had the same retention time and the mass spectrum (Fig. 3) is identical, apart from background noise, to that obtained from diltiazem hydrochloride. An interpretation of the spectrum is proposed in Table 2.

Subsequent experiments were carried out by selected ion recording at ions charateristic of *N*-chlorodimethylamine (m/z 42, 78 and 79). A representative chromatogram is presented in Fig. 4; the relative peak heights do not correspond to those of the scanned spectrum, because no adjustment was made for the variation of the transmission of the quadrupole filter as a function of the m/z ratio. The peak surface areas given in the tables are for m/z 78.

The absolute signal intensity and the ratio of peak height to baseline noise varied widely during the course of the investigation. The detection limit ($S/N = 3$) was usually < 10 ppm of DMC with respect to the compound being examined (final concentration < 100 ng/ml).

All eight batches of diltiazem hydrochloride examined, whether from Synthélabo or from other manufacturers, gave a peak corresponding to *N*-chlorodimethylamine on at least one occasion. The peak was weak or absent unless the vial had been agitated during equilibration (ultrasonically before heating in the manual method, mechanically during heating in the automatic injector). Even with agitation, the peak area varied widely. The results presented for one batch of diltiazem hydrochloride in Table 1 illustrate the degree of variability that was observed for consecutive injections of this compound.

3.2. Formation of the artefact from DMC

Among potential impurities of diltiazem hydrochloride, the synthetic reagent DMC was in-

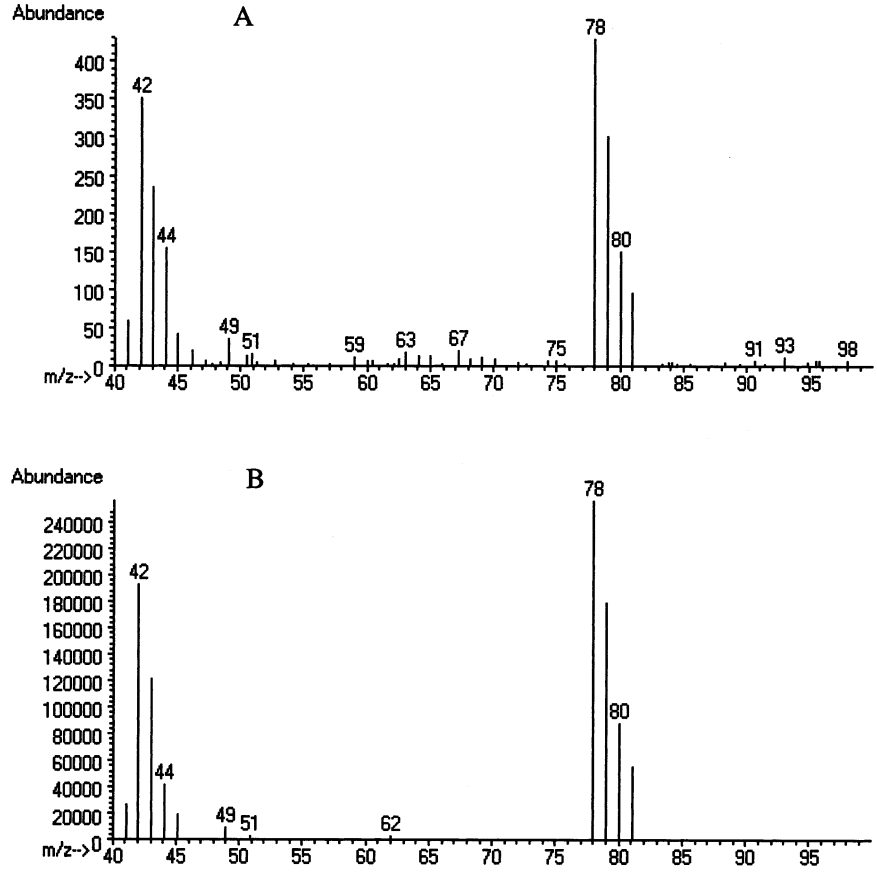

Fig. 3. Mass spectra of artefact from diltiazem hydrochloride (A) and of *N*-chlorodimethylamine (B).

vestigated, in the presence and absence of the drug substance. *N*-chlorodimethylamine was detected in all experiments and at all concentrations investigated (1–100 ppm), whether or not the solution was agitated. The identity of the peak was confirmed by its mass spectrum (not shown). The peak surface area was not, however, reproducible within a factor of 2, and as explained above the detection limit was variable.

On one occasion, the area of the *N*-chlorodimethylamine peak diminished towards the end of a long series of runs with the automatic injector. The response was restored by exhaustively steam-cleaning the flow-lines, a treatment which presumably re-passivates the nickel surfaces.

In view of the volatility, reactivity and toxicity of *N*-chlorodimethylamine, and the variability in the results for DMC, no attempt was made to evaluate the amount formed per mole of DMC. However, it can be judged from the intensity of the peaks that the reaction yield would be well above trace levels. As explained above, the amount of *N*-chlorodimethylamine formed from diltiazem hydrochloride varied from one injection to the next; it corresponded to the amounts of DMC ranging from undetectable to several hundred ppm (Table 1).

3.3. Origin of *N*-chlorodimethylamine

The following experiments demonstrate that the dimethylamino group of *N*-chlorodimethylamine

is derived exclusively from the solvent dimethylformamide, and not from DMC:

(1) A mixture of 1000 ppm DMC in 1 ml unlabelled dimethylformamide and 0.75 ml [$^2H_7$]-dimethylformamide gave the spectrum presented in Fig. 5. This spectrum (interpretation: Table 2) is consistent with a mixture of [$^2H_6$]-labelled and unlabelled *N*-chlorodimethylamine, and there was no evidence for exchange of individual deuterium atoms or methyl groups.

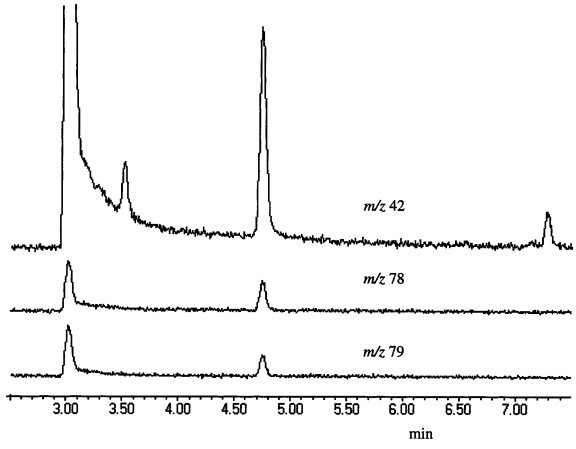

Fig. 4. Selected ion recording chromatogram of diltiazem hydrochloride (stock solution 4, injection 2; Table 1). The retention time of *N*-chlorodimethylamine is 4.75 min.

Table 1
Peak surface areas for *N*-chlorodimethylamine obtained for repeated analyses of a batch of diltiazem hydrochloride, and for a reference solution of DMC[a]

Product	Stock solution	Peak surface area
DMC (100 ppm reference)		26241
		17319
Diltiazem hydrochloride	1	n.d.
		65643
	2	16047
		27614
	3	56739
		3923
	4	7034
		39708
	5	n.d.
		26040
	6	21595
		67347

[a] The automatic head-space injector was used. n.d., not detected (detection limit <10 ppm DMC).

The peaks corresponding to labelled dimethylformamide are relatively less intense than would be expected from the composition of the solvent mixture (42% v/v labelled solvent). This effect is in fact more marked than would appear from the spectrum shown, which was taken at the maximum of the peak of the labelled compound, which occurred (as expected) several seconds before that of the unlabelled compound. Experiments carried out with pure [$^2H_7$]-dimethylformamide did not yield detectable amounts of *N*-chlorodimethylamine.

(2) The inverse experiment was carried out, using a homologue of DMC, *N*,*N*-diethylaminoethyl chloride, in unlabelled dimethylformamide; labelled DMC is not available. The spectrum of *N*-chlorodiethylamine (not shown) has a molecular ion of m/z 107 and a relatively intense fragment of m/z 92. No peak was detected at the retention time of this compound when the m/z 92 fragment was monitored. Only one GC peak was detected, and this corresponded to *N*-chlorodimethylamine (Fig. 6).

(3) Finally, it was found that *N*-chlorodimethylamine is formed during headspace analysis of dimethylformamide to which has been added 5 μl of concentrated aqueous HCl (not shown), although this reaction was somewhat less reproducible than that given by DMC.

3.4. Formation of the artefact from other hydrochlorides

Six drug substances in the form of hydrochlorides were examined, together with triethylamine (Table 3). Five of these compounds gave a positive response on at least one occasion.

Tris(hydroxymethyl)aminomethane hydrochloride (Tris–HCl) was investigated on a different occasion. A strong response was obtained for each of five injections, and the mean peak surface area corresponded to 380 ppm DMC.

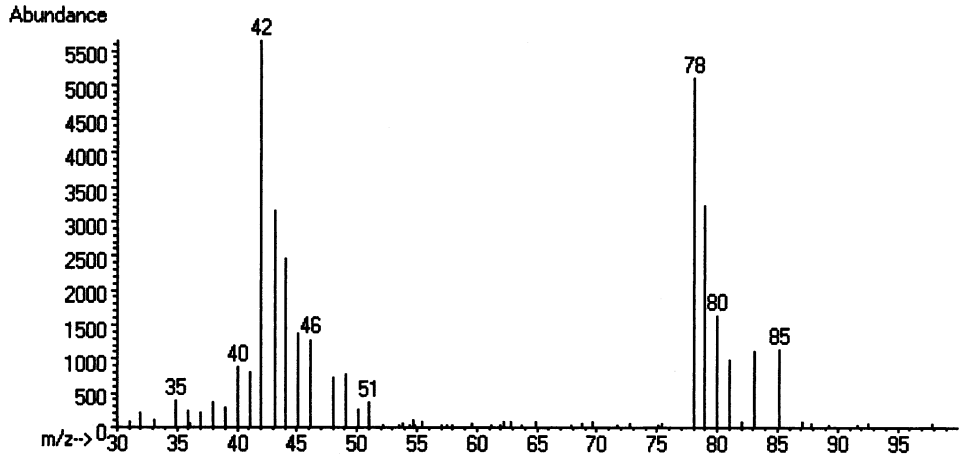

Fig. 5. Mass spectrum obtained by GC/MS headspace analysis of a mixture of $[^2H_7]$-dimethylformamide and unlabelled dimethylformamide containing… ppm DMC.

3.5. Pressure in headspace vial

After some (but not all) of the above experiments in which DMC was not detected, it was found that the crimp seal of the headspace vial had become loosened, apparently as a result of excessive pressure. Three vials containing neat dimethylformamide were prepared with the standard flat teflon-lined septa (Perkin Elmer cat. B010-4241), and three other vials were sealed with less inert but more tightly-fitting septa (Hewlett–Packard cat. 250 030). The vials were heated at 105°C for 45 min in the automatic injector, which was then opened. The pressure in the vials was measured by means of a bourdon gauge supplied for this purpose with the Perkin Elmer HS40 injector. The pressure measured in all vials was close to 15 psi ($\sim$1 bar); the actual pressure would be somewhat greater than this, because of the volume of the gauge.

4. Discussion

4.1. Artefact

Under the conditions prescribed by the European Pharmacopeia (1999a), dimethylformamide is degraded to *N*-chlorodimethylamine in the presence of a small concentration of hydrochloric acid. Neither this nor any similar reaction appears to have been described in the literature. An oxidation is involved, since the formation of chloramines requires the presence of 'positive chlorine', but whether the primary oxidising agent is air or an oxidative degradation product of the dissolution solvent has not been established. Air may participate in the formation of the artefact, at least from diltiazem hydrochlo-

Table 2
Interpretation of mass spectrum of the head-space vapour of a vial containing a solution of DMC in a mixture of $[^2H_7]$-dimethylformamide and unlabelled dimethylformamide

m/z	Interpretation
42	$[CH_2{=}N{=}CH_2]^+$ (d_0)
43	$[CH_2{=}N{-}CH_3]^{+\cdot}$ (d_0)
44	M–Cl
45	$[CH_3{-}NH{-}CH_3]^{+\cdot}$?
46	$[CD_2{=}N{=}CD_2]^+$
48	$[CD_2{=}N{-}CD_3]^{+\cdot}$
49	$[^{35}Cl{=}CH_2]^+$
51	$[^{37}Cl{=}CH_2]^+ + [^{35}Cl{=}CD_2]^+$ ($+[CD_3{-}NH{-}CD_3]^{+\cdot}$?)
78	$[M{-}H]^+$ (d_0)
79	$M^{+\cdot}$ (d_0)
80	$[M{-}H]^+$ (d_0, ^{37}Cl)
81	$M^{+\cdot}$ (d_0, ^{37}Cl)
83	$[M{-}D]^+$ (d_6)
85	$M^{+\cdot}$ (d_6)
87	$M^{+\cdot}$ (d_6, ^{37}Cl)

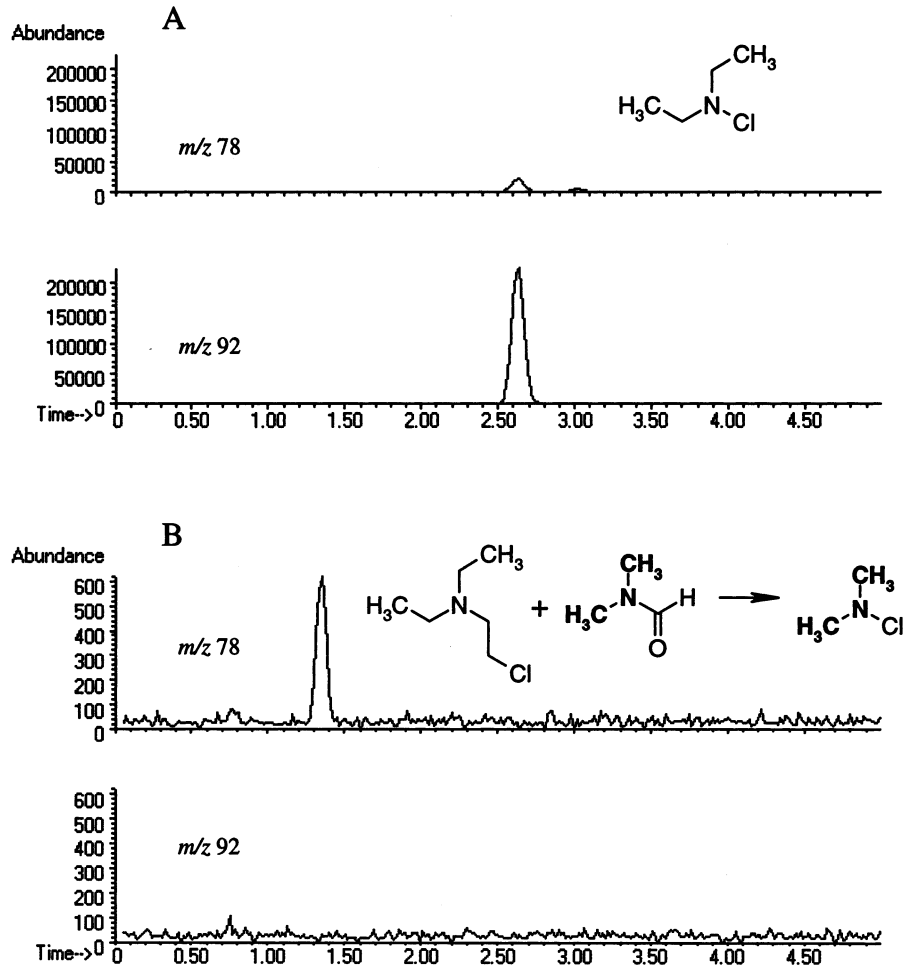

Fig. 6. Selected ion recording chromatogram of *N*,*N*-diethylaminoethyl chloride in dimethylformamide. The ion of m/z 78 is characteristic of *N*-chlorodimethylamine (retention time 1.4 min), and the ion of m/z 92 of *N*-chlorodiethylamine (retention time 2.65 min).

ride, because, in vials that had not been ultrasonicated, agitation is required during equilibration. However, agitation is not required in the case of DMC, and a different mechanism may be involved. Some experiments were carried out in which the vials were purged with oxygen or argon, but the results were inconclusive because of the inherent lack of repeatability of the artefact formation.

The fact that *N*-chlorodimethylamine was not detected in all experiments can be explained in part by its reactivity; in particular, the compound would be expected to react with metal surfaces. On some apparently random occasions, the crimp seal of the headspace vial appears to have failed, presumably under the pressure of gaseous decomposition products of dimethylformamide. Neat dimethylformamide was shown to be sufficiently

stable at 105°C, but this does not exclude the possibility that some analytes could catalyse its decomposition to carbon monoxide and dimethylamine.

The results obtained with deuterium labelled dimethylformamide and *N*,*N*-diethylaminoethyl chloride demonstrate conclusively that the *N*-chlordimethylamine formed is derived exclusively from dimethylformamide, and that there is no significant exchange of hydrogens or methyl groups. This is confirmed by the result obtained with a homologue of DMC in unlabelled dimethylformamide. The unusually strong isotope effect in favour of unlabelled dimethylformamide is of some interest; while it would be due in part to reduced volatility of deuterated *N*-chlorodimethylamine, there is almost certainly a large difference in reactivity, in particular, neat labelled dimethylformamide appeared not to react at all in several experiments. It could therefore be speculated that the formation of labelled *N*-chlorodimethylamine in the solvent mixture is due to a reactive intermediate that is formed in significant amounts only from unlabelled dimethylformamide. Presumably, cleavage of the aldehydic hydrogen would be involved in such a scheme.

Table 3
Peak surface areas for *N*-chlorodimethylamine obtained for various hydrochlorides, and for a reference solution of DMC[a]

Compound	Sample	Peak surface area
DMC (100 ppm reference)		15389
(Compound under development)	1	n.d.
pK_a 8.0	2	n.d.
	3	n.d.
	4	n.d.
	5	n.d.
Lintopride–HCl	1	7357
pK_a 10.3	2	n.d.
	3	n.d.
Metoclopramide–HCl	1	n.d.
pK_a 9.7	2	n.d.
	3	n.d.
Eliprodil–HCl	1	n.d.
p$K_a \sim 9.1$	2	n.d.
	3	n.d.
	4	8367
	5	n.d.
(Compound under development)	1	Trace
pK_a 7.3	2	3583
Tiapride–HCl	1	45236
pK_a 9.2	2	n.d.
Triethylamine–HCl	1	n.d.
pK_a 10.9	2	n.d.
	3	7784

[a] The automatic head-space injector was used. n.d., not detected (detection limit <10 ppm DMC).

While DMC gives a high yield of *N*-chlordimethylamine, the formation of the latter compound when diltiazem hydrochloride is heated in DMF is not evidence for the presence of DMC. The results presented exclude any possibility that the dimethylamino moiety of *N*-chlorodimethylamine might be derived from DMC.

Dimethylformamide to which had been added a small amount of concentrated aqueous HCl also yielded *N*-chlordimethylamine. If it is assumed for the purpose of this discussion that artefact formation is due in all cases to the presence of free HCl, the formation of *N*-chlorodimethylamine from DMC could be explained by the release of HCl associated with the cyclisation of DMC to give the dimethylaziridinium ion (Fig. 2).

Free HCl may also be formed by partial dissociation of hydrochloride salts, or by an oxidative or other degradation of their basic functions. Several other hydrochlorides were examined. Although, as with diltiazem hydrochloride, *N*-chlorodimethylamine was not detected in all vials examined, six of eight hydrochlorides of differing structures gave a positive result for the artefact on at least one occasion. Nevertheless, diltiazem hydrochloride yielded *N*-chlordimethylamine more consistently than the other hydrochlorides except Tris, a finding that could be explained in terms of hydrolysis of the *O*-acetate function of this compound by traces of water. Because HCl is a relatively weak acid in solvents of low basicity and in the strict absence of water, the acetic acid generated would release a certain amount of undissociated HCl.

There is no evidence from the results presented for an association between the yield of *N*-chlorodimethylamine and the aqueous dissociation constants or polarities of the compounds studied.

4.2. Analysis of diltiazem hydrochloride for DMC

As explained in Section 1, it is necessary to exclude any possibility that production batches of diltiazem hydrochloride contain significant amounts of DMC. The norm applied by this laboratory is not more than 1 ppm.

When considering methods for the determination of DMC, account must be taken of an extensive literature which demonstrates that the reactive intermediate in all alkylations by β-chloro-*N*,*N*-dialkylethylamines that have been investigated is the corresponding dialkylaziridiunium ion DMA (Golumbic et al., 1946; Cohen et al., 1948; Allen and Chapman, 1960; Hansen, 1962). The kinetics of formation of DMA (Fig. 2) from DMC in aqueous solution have been studied by Simonetta et al. (1949).

As suggested earlier, the HCl generated may, by an unknown mechanism, lead to the degradation of dimethylformamide to *N*-chlorodimethylamine. Because the reaction is reversible in the presence of chloride ion (Levins and Papanastassiou, 1965), any residue of the alkylating agent in diltiazem hydrochloride is likely to be in the form of DMC, but this remains to be proven.

Halogenated alkylamines are synthetic starting materials for numerous drug substances, but only one method appears to have been published for the determination of these highly toxic compounds (Leigh and Bowker, 1991). These authors hydrolysed the compounds to the corresponding alcohols, which were separated by TLC after derivatisation. Some further development would be required in order to obtain a detection limit below 1 ppm. The major disadvantage of this approach is that innocuous traces of the aminoalcohols already present in the product being examined would give false positive results.

In this laboratory, diltiazem hydrochloride has been analysed by several unpublished methods. DMC base is amenable to GC after extraction in a non polar solvent, whereas the sum of the DMC and DMA concentrations can be determined by means of the standard reagent for alkylating agents 4-(4-nitrobenzyl)pyridine (NBP; Dictionary of Analytical Reagents, 1993). To date, no production batch of diltiazem hydrochloride, from whatever source, has been found to contain more than 1 ppm of alkylating agent. Following the discovery of the artefactual formation of *N*-chlorodimethylamine during head-space analysis, a direct LC/MS method was developed for the individual determination of DMC and DMA. The results obtained confirm the earlier findings. These analytical methods are currently under review, with the aim of establishing a compendial method; details will be published at a later date.

Traces of DMC base can be detected by headpace analysis of a relatively concentrated solution of the hydrochloride in dimethylformamide (>100 ppm; results not shown). The size of the peak will be a function of the amount of the impurity dimethylamine already present or formed by degradation of dimethylformamide; the estimated pK_a of DMC in aqueous solution is 8.4. Whatever the dissolution solvent, direct headspace analysis is unlikely to be applicable to the assay of DMC in diltiazem hydrochloride, because under the necessary basic conditions, DMC would react with the side-chain nitrogen of diltiazem. It should be noted that the European Pharmacopeia (1999b) does not prescribe the addition of acid or base, despite the listing of acetic acid and pyridine as solvents to be searched for.

4.3. Suitability of dimethylformamide and alternative solvents

It is clear from the results presented here that dimethylformamide in unsuitable as a general-purpose solvent for head-space analyses, at least at the temperature prescribed (105°C). Since the norms for some volatile impurities are as low as 2 ppm, even traces of artefactual volatile compounds are a source of difficulty. Quite likely, a lower temperature would be suitable in the majority of cases, since achieving a satisfactory detection limit is rarely a serious source of difficulty except for the least volatile impurities, even when

using columns of 0.32 mm i.d. If necessary, wider columns can be used in order to obtain a more favourable split ratio.

While there is no doubting the need for a general compendial method, the European Pharmacopeia (1999a) is, in our opinion, too prescriptive in the choice of dissolution solvent and equilibration conditions; these details are specific to the substance being examined, and should perhaps be left to the individual monographs. In addition, the list of potential impurities to be searched for (European Pharmacopeia 1999b) is of doubtful utility, since it does not include volatile impurities other than residual solvents. For example, hydrochlorides of basic drug substances can become contaminated by chloroalkanes generated by reaction of HCl with alcohols or ethers, a reaction that has been observed during recrystallisation as well as storage in the presence of trace residual solvent (unpublished results). Other impurities not listed include relatively involatile impurities of recrystallisation solvents, such as higher homologues and the condensation products of ketones, which tend to become concentrated in some drug substances.

There is little published information on the choice of dissolution solvents for head-space analysis. Useful solvents not mentioned in the general method are benzyl alcohol (Bicchi and Bertolino, 1982), and *N*,*N*-dimethylacetamide (Mulligan and McCauley, 1995; George and Wright, 1997; Hong and Altorfer, 1997). A pure grade of 2-methoxyethanol, stored over 3 Å molecular sieve in order to limit the concentration of methanol, has been found in this laboratory to be one of the most generally useful solvent other than water. Unfortunately, it is now considered unsuitable for this application, as it is teratogenic and would be released into the atmosphere in case of vial seal failure. Various propane diol derivatives could be investigated as alternatives.

5. Conclusions

The results presented in this paper demonstrate that dimethylformamide is unsuitable as a general-purpose dissolution solvent for the head-space GC determination of volatile impurities. Alternative solvents could be considered, but it would be more appropriate to indicate the solvent and operating conditions in the individual monographs rather than in the general method.

The fact that both diltiazem hydrochloride and the alkylating agent DMC used in its synthesis generate the same artefact in the presence of dimethylformamide does not indicate that the drug substance contains significant amounts of DMC; in fact, the hydrochlorides of several other bases give the same reaction. Concentrations of DMC in production batches of diltiazem hydrochloride have always been < 1 ppm.

Acknowledgements

D. Tessier for technical assistance, M. Dimsdale, M. Gaspar, F.-X. Jarreau and A. Wick for helpful discussions.

References

Allen, J.F., Chapman, N.B., 1960. Di-*N*-substituted 2-halogenoethylamines. Part III. *N*-2(or 3 or 4)-chlorobenzyl-*N*-ethyl derivatives: synthesis, reactivity, and pharmacology. J. Chem. Soc. 1482–1487.

Bicchi, C., Bertolino, A., 1982. Determination of residual solvents in drugs by head-space gas chromatography. Farmaco Ed. Pr. 37, 88–97.

Cohen, B., Van Artsdalen, E.R., Harris, J., 1948. Reaction kinetics of tertiary β-chloroethylamines in dilute aqueous solution. I. The cyclization process. J. Am. Chem. Soc. 70, 281–285.

Dictionary of Analytical Reagents, 1993. Reagent N-00139, Chapman and Hall, London, p. 739.

European Pharmacopeia, 1999a. Identification and control of residual solvents. In: European Pharmacopeia Supplement 1999, European Department for the Quality of Medicines within the Council of Europe, Strasbourg, section 2.4.24, pp. 14–18.

European Pharmacopeia, 1999b. Residual solvents. Limiting residual solvent levels in active substances, excipients and medicinal products. In: European Pharmacopeia Supplement 1999, European Department for the Quality of Medicines within the Council of Europe, Strasbourg, section 5.4, pp. 205–212.

George, R., Wright, P.D., 1997. Analysis of USP organic volatile impurities and thirteen other common residual solvents by static headspace analysis. Anal. Chem. 69, 2221–2223.

Golumbic, C., Fruton, J.S., Bergmann, M., 1946. Chemical reactions of the nitrogen mustard gases. I. The transformations of methyl-bis(β-chloroethyl)amine in water. J. Org. Chem. 11, 518–535.

Hansen, B., 1962. Kinetics of formation and reactions of quaternary ethylenimonium compounds. Acta Chem. Scand. 16, 1945–1955.

Hong, L., Altorfer, H.R., 1997. A comparison study of sample dissolution media in headspace analysis of organic volatile impurities in pharmaceuticals. Pharm. Acta Helv. 72, 95–104.

Leigh, P.H., Bowker, M.J., 1991. Simple procedure involving derivatisation and thin-layer chromatography for the estimation of trace levels of halogenated alkylamines and their hydrolysis products in drug substances and formulations. J. Chromatogr. 543, 211–219.

Levins, P.L., Papanastassiou, Z.B., 1965. A nuclear magnetic resonance study of the 2-haloethylamines. J. Am. Chem. Soc. 87, 826–831.

Mulligan, K.J., McCauley, H., 1995. Factors that influence the determination of residual solvents in pharmaceuticals by automated static headspace sampling coupled to capillary GC-MS. J. Chromatogr. Sci. 33, 49–54.

Simonetta, M., Visconti di Modrone, N, Favini, G., 1949. Azione mutagena delle sostanze chimiche. Nota IV. Sulla cinetica delle reazioni tra dimetil-β-chloroetilammina e acqua. Gazz. Chim. Ital. 80, 129–139.