Note

Temperature-Dependent Formation of *N*-Nitrosodimethylamine during the Storage of Ranitidine Reagent Powders and Tablets

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The purpose of this study was to elucidate the effect of high-temperature storage on the stability of ranitidine, specifically with respect to the potential formation of *N*-nitrosodimethylamine (NDMA), which is classified as a probable human carcinogen. Commercially available ranitidine reagent powders and formulations were stored under various conditions, and subjected to LC-MS/MS analysis. When ranitidine tablets from two different brands (designated as tablet A and tablet B) were stored under accelerated condition (40 °C with 75% relative humidity), following the drug stability guidelines issued by the International Conference on Harmonisation (ICH-Q1A), for up to 8 weeks, the amount of NDMA in them substantially increased from 0.19 to 116 ppm and from 2.89 to 18 ppm, respectively. The formation of NDMA that exceeded the acceptable daily intake limit (0.32 ppm) at the temperature used under accelerated storage conditions clearly highlights the risk of NDMA formation in ranitidine formulations when extrapolated to storage under ambient conditions. A forced-degradation study under the stress condition (60 °C for 1 week) strongly suggested that environmental factors such as moisture and oxygen are involved in the formation of NDMA in ranitidine formulations. Storage of ranitidine tablets and reagent powders at the high temperatures also increased the amount of nitrite, which is considered one of the factors influencing NDMA formation. These data indicate the necessity of controlling/monitoring stability-related factors, in addition to controlling impurities during the manufacturing process, in order to mitigate nitrosamine-related health risks of certain pharmaceuticals.

Key words *N*-nitrosodimethylamine (NDMA); ranitidine; forced degradation; storage; impurity

Introduction

In 2018, the finding of *N*-nitrosodimethylamine (NDMA) and other nitrosamines in multiple valsartan and angiotensin II receptor blocker (ARB) formulations triggered concern about trace impurities of probable human carcinogens in these widely used pharmaceutical products.[1)] Regulatory agencies collaborated to analyze impurities in the products, investigate the cause, and enact several measures, including establishment of interim criteria for distribution, in order to mitigate the potential risk. Analysis by HPLC, GC-MS, and/or LC-MS/MS indicated unacceptable amounts of NDMA in some active pharmaceutical ingredients (APIs) and their drug products.[2–5)] Interim criteria to control the levels of mutagenic impurities (*e.g.*, NDMA and *N*-nitrosodiethylamine (NDEA)) were established on the basis of acceptable daily exposure limits to the particular compound and the drug's maximum daily dose, following the International Conference on Harmonisation (ICH) M7 guideline.[1,6–8)]

Ranitidine and other H2-receptor antagonists (*e.g.*, nizatidine) represent another group of pharmaceuticals with similar nitrosamine contamination issue.[9)] In 2019, multiple products were recalled from the market after varying amounts of NDMA were found in some APIs and tablets.[9–12)] The intrinsically unstable nature and ternary amine structure of ranitidine raised some questions regarding the cause of impurity found in the products; it is of particular interest whether the NDMA is formed during storage of solid formulations of ranitidine HCl (Fig. 1). Ranitidine HCl readily degrades during the storage of the solids at elevated temperature and humidity.[13–16)] The stability of ranitidine APIs and formulations had been assessed using accelerated stress tests during drug development in the 1980s, but the risk of formation of NDMA impurities at sub-ppm levels was not explored. The potential of NDMA formation during storage was suggested in an Australian regulatory report in 2019. The report showed that some products that were nearing their expiration dates had higher levels of NDMA than products that were newer.[10)] The observation of elevated NDMA level by GC-based analysis of ranitidine products in another study also suggested degradation-related NDMA formation from ranitidine.[17)] Forced degradation studies, especially those profiling degradation products, performed under relevant stress conditions are expected to provide valuable information for predicting potential drug changes during storage at ambient temperatures.[18)] However, to the best of our knowledge, no experimental data have been reported on possible NDMA formation during the storage of ranitidine formulations.

Several theories have been proposed regarding factors affecting NDMA formation. The European Medicines Agency (EMA) reported that NDMA could be generated when dimethylamine released from ranitidine is exposed to a source of nitrite (*e.g.*, sodium nitrite).[19)] Environmental health studies have reported that chloramination of water leads to the production of NDMA from ranitidine and other tertiary amine

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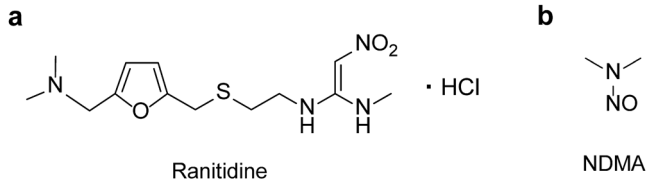

Fig. 1. Chemical Structure of (a) Ranitidine HCl and (b) *N*-Nitrosodimethylamine (NDMA)

compounds.[20–23] There are also conflicting reports regarding possible NDMA formation due to the reaction of ranitidine with nitrite in the gastrointestinal tract after oral ingestion.[9,24]

In the present study, forced degradation of ranitidine HCl-containing reagent powders and ethical tablet formulations, which were commercially available in Japan, was performed for short durations under high-temperature storage conditions to assess possible NDMA formation.

Experimental

Chemicals and Reagents The NDMA standard (>99.0% purity) was purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan), and deuterium-labeled NDMA (NDMA-d_6), the internal standard (IS), was purchased from AccuStandard (New Haven, CT, U.S.A.). Ranitidine HCl reagent powders were obtained from Cayman Chemical (Ann Arbor, MI, U.S.A.) and Toronto Research Chemicals (Toronto, Ontario, Canada). Two pharmaceutical formulations of ranitidine tablet 150 mg, which are commercially available in Japan, were also used in this study. Methanol and dimethyl sulphoxide (DMSO) were purchased from Kanto Chemical Corporation (Tokyo, Japan). Acetonitrile, formic acid, ammonium acetate, and the nitrite reference standard were purchased from FUJIFILM Wako Pure Chemical Corporation.

Storage of Samples at High Temperatures Ranitidine tablets in push-through packages and ranitidine reagent powders (approximately 250 mg) in glass vials with hermetic caps were stored in a storage chamber (CSH-112, Espec Crop., Osaka, Japan) controlled at 40 or 50 °C with 75% relative humidity (RH) for up to 8 weeks. For a subset of ranitidine reagent powders (vacuumed sample), the headspace air in the vial was removed by using a freeze dryer (FreezZone 6; Labconco, Kansas City, MO, U.S.A.). Ranitidine reagent powders kept in open, hermetically sealed (closed), and vacuum vials were then subjected to a forced-degradation study under high-temperature conditions (60 °C/50% RH) for 1 week.

Headspace-GC-MS (HS-GC-MS) Analysis Ranitidine tablets were ground to a fine powder using an agate mortar and 250 mg of the tablet powder was weighed into a 10-mL headspace vial. One hundred and twenty-five microliters of NDMA-d_6 solution (10 μg/mL in DMSO) and DMSO was added to vial to make a total volume of 2.5 mL and the vial was immediately capped and crimped. The vial was shaken for 30 min using a mechanical shaker, and then subjected to HS-GC/MS analysis.

NDMA was analyzed using a GC-MS system (7890B/5977B; Agilent Technologies, Palo Alto, CA, U.S.A.) operated in the electron ionization mode (70 eV). The headspace oven temperature was operated isothermally within the range of 80–110 °C for 10 min. The vial equilibration and injection times were set at 10 and 1 min, respectively. The GC injector was operated at 220 °C with a 5 : 1 split ratio. Helium was used as the carrier gas at a constant flow rate of 3 mL/min. A DB-WAX capillary column (30 m × 0.25 mm, film thickness: 0.25 μm; Agilent Technologies) was used with the following oven program: hold at 70 °C for 4 min, ramp from 70 to 110 °C at 10 °C/min, ramp from 110 to 240 °C at 20 °C/min, and then held at 240 °C for 2 min. The MS transfer line temperature was maintained at 250 °C. The mass spectrometer was operated in the selected ion monitoring (SIM) mode. For NDMA detection, *m*/*z* 42 and 74 were used for confirmation and quantification, respectively. For NDMA-d_6 detection, *m*/*z* 46 and 80 were used for confirmation and quantification, respectively.

Table 1. Multiple Reaction Monitoring Transition for NDMA and NMDA-d_6

Analyte	Precursor ion (*m*/*z*)	Product ion (*m*/*z*)	Q1 Pre bias	Collision energy	Q3 Pre bias
NDMA	75.09	43.10	−15.0	−18.0	−15.0
NDMA-d_6 (IS)	81.09	46.15	−15.0	−16.0	−16.0

LC-MS/MS Analysis Approximately 75 mg of ranitidine reagent powder was weighed into a polypropylene tube and 0.25 mL of NDMA-d_6 solution (25 μg/mL in 20% methanol) and 1.0 mL of 20% methanol were added. Two ranitidine tablets (150 mg each) were placed in a polypropylene tube and 1.0 mL of NDMA-d_6 solution (25 μg/mL in 20% methanol) and 4.0 mL of 20% methanol were added. After vigorous shaking followed by centrifuge filtration using a 0.22-μm centrifugal filter unit (Ultrafree-MC-GV polyvinylidene difluoride (PVDF); Merck Millipore, Billerica, MA, U.S.A.), the amount of NDMA present in the filtrate was determined by LC-MS/MS.

LC separations were performed on a Nexera LC-40 ultra-high performance liquid chromatography system (Shimadzu, Kyoto, Japan) with a Shimpack ARATA C18 column (3.0 × 75 mm, 2.2-μm particle size, 12-nm pore size). Mobile phase A consisted of water–acetonitrile–formic acid (990 : 10 : 1, v/v/v) and mobile phase B consisted of water–acetonitrile–formic acid (100 : 900 : 1, v/v/v). The flow rate and column temperature were 450 μL/min and 40 °C, respectively, and the injection volume was 5 μL. A linear gradient was used for elution, consisting of mobile phase B from 0 to 1% in 1 min, 1 to 30% in 0.25 min, and 30% for 1.25 min. The column was then equilibrated for 4 min with mobile phase A. Mass spectrometric detection was performed on a Shimadzu LCMS8060 tandem mass spectrometer with an electrospray ionization source in the positive ion mode. The nebulizer gas flow rate was 3 L/min. The interface, desolvation tube, and heating block temperatures were 300, 250, and 400 °C, respectively, and the drying gas flow rate was 10 L/min. Multiple reaction monitoring transitions for the analytes are shown in Table 1.

The method was linear ($R^2 > 0.999$) in the range of 1–50000 ng/mL. The limit of quantification (LOQ) was 1 ng/mL (0.03 ppm) with a signal-to-noise (*S*/*N*) ratio of ≥10. The recovery rate of NDMA spiked at three concentrations (3.5, 10, and 50 ng/mL) was 93–102%, with a relative standard deviation of 0.26–0.99% ($n = 3$).

Ion Chromatography Analysis Ranitidine tablets and powders dissolved in purified water (3 mg/mL) were dechlorinated using a MetaSep Ag SPE column (GL Sciences, Tokyo,

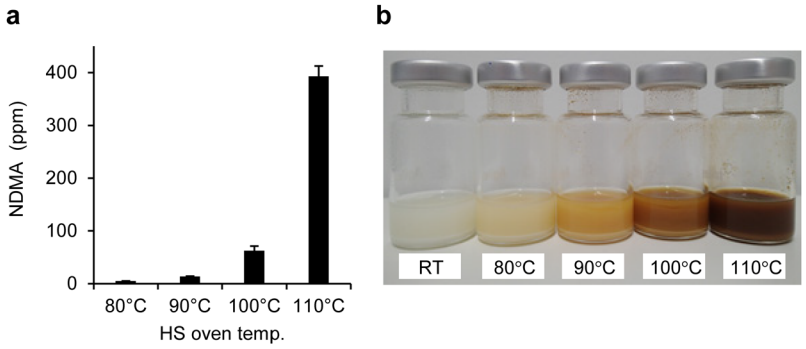

Fig. 2. Effect of Headspace Oven Temperature on HS-GC-MS Analysis of NDMA in Ranitidine Tablets

(a) Amount of NDMA produced under various heating conditions in the headspace (HS) oven. Each result represents the mean ± standard deviation (S.D.) ($n = 3$). (b) Changes in visual appearance after 10 min of HS oven equilibration at various temperatures. (Color figure can be accessed in the online version.)

Japan), and then centrifuged with a 0.22-μm centrifugal filter unit (Ultrafree-MC-GV PVDF). Nitrite ion levels in the filtrates were determined by ion chromatography using a Dionex Integrion HPIC System (Thermo Scientific, San Jose, CA, U.S.A.) equipped with an IonPac AG19-4 μm guard column (4 × 50 mm), an IonPac AS19-4 μm anion exchange column (4 × 250 mm), an anion dynamically regenerated suppressor (4 mm), and a UV detector (214 nm). Ten microliters of sample was used for all injections. The mobile phase was produced using an electrodialytic potassium hydroxide (KOH) eluent generator. For KOH gradient elution, the concentration was maintained at 20 mM for the first 12 min, increased to 80 mM over 4 min, and then maintained for 14 min. The flow rate and column temperature were 0.8 mL/min and 30 °C, respectively. A six-point calibration curve of nitrite ion standard was prepared from 0.005 to 1.0 ppm for which the R^2 values were >0.999. The LOQ of this method was estimated to be 1.67 ppm with an S/N ratio of ≥10.

Results and Discussion

Rapid Forced-Degradation Study by HS-GC-MS The HS-GC-MS analysis was initially used to clarify the cause for a high amount of NDMA being found on GC-MS analysis of ranitidine tablets in previous report.[17] Figure 2a shows the amount of NDMA detected under various heating conditions (80–110 °C) in the headspace oven for 10 min. The amount of NDMA sharply increased upon exposure to temperatures above 100 °C. Browning of the formulation was also observed in a temperature dependent manner (Fig. 2b). These data indicate that ranitidine decomposes on heating and that NDMA is generated during headspace equilibration. The results confirmed that HS-GC-MS is not suitable for the accurate quantification of NDMA because sample heating generates NDMA in the extremely high-temperature headspace and/or other part of the systems. However, HS-GC-MS may provide a simple method for rapid screening of other drugs that has potential risk of NDMA formation. For example, the HS-GC-MS analysis of nizatidine, which is structurally similar to ranitidine, showed an apparent formation of NDMA by heating at 130 °C (Fig. S1). Nizatidine may be more thermostable than ranitidine, as the amount of NDMA generated by heating of nizatidine tablet was much lower than that obtained with ranitidine. In the subsequent experiments, we performed LC-MS/MS analysis to avoid heat treatment-induced sample decomposition during the measurement.

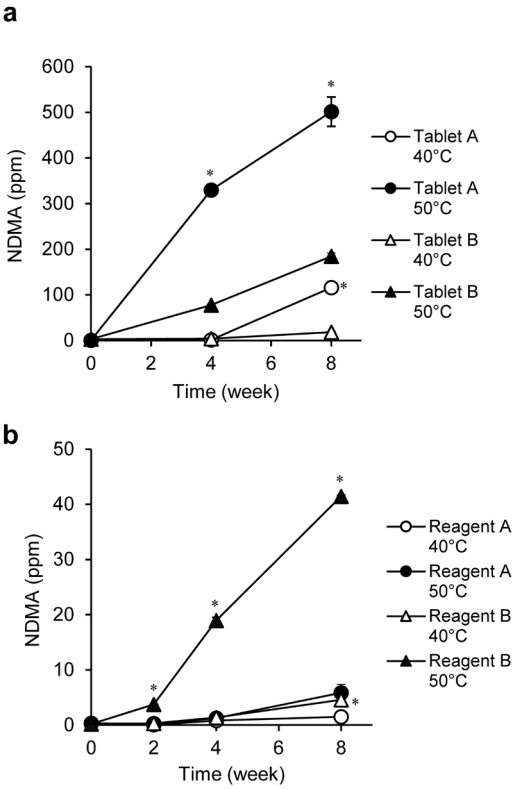

Fig. 3. NDMA Formation in Ranitidine Samples during 8 Weeks of Storage under Accelerated and Stress Conditions

The amount of NDMA in (a) ranitidine tablets and (b) ranitidine reagent powders stored at 40 °C/75% RH or 50 °C/75% RH were measured by LC-MS/MS. Each result represents the mean ± S.D. ($n = 3$). *$p < 0.005$; (a) *vs.* tablet B, (b) *vs.* reagent A compared at the same storage conditions by Student's *t*-test.

NDMA Formation from Ranitidine under Accelerated Stress Conditions The potential formation of NDMA during the storage of ranitidine tablets and reagent powders was evaluated under accelerated stress conditions following the guidelines issued by the ICH. According to the notifications from the Ministry of Health, Labour and Welfare of Japan and the U.S. Food and Drug Administration (FDA), the accepted daily intake limit for NDMA in ranitidine drug substance was set to be 0.32 ppm (0.32 μg of NDMA in 1 g of ranitidine) based on the maximum daily dose of ranitidine (300 mg/d).[12,25] Two ranitidine tablet formulations found to have NDMA levels below (tablet A) and above (tablet B) the limit in preliminary

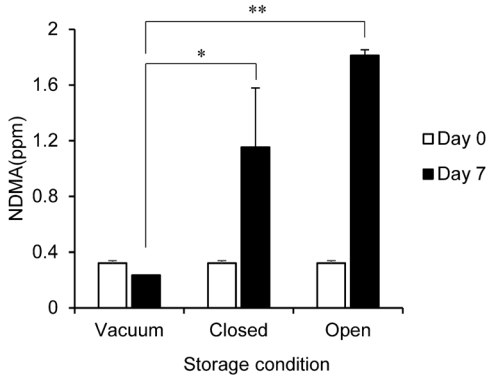

Fig. 4. Forced-Degradation Study of Ranitidine Reagent Powder A Stored under Various Environmental Conditions at 60 °C

Ranitidine reagent powders were stored in glass vials with (closed) or without (open) caps at 60 °C/50% RH and was then subjected to NDMA measurement by LC-MS/MS. Samples devoid of moisture/oxygen (vacuum) were also used in this study. Each result represents the mean ± S.D. ($n = 3$). *$p < 0.05$; **$p < 0.001$; compared with the vacuum sample on each day by Student's *t*-test.

Table 2. Amount of Nitrite Ion in Ranitidine after High-temperature Storage for 8 Weeks

Storage conditions	Nitrite ion (ppm)		
	Day 0	8 weeks 40 °C/75% RH	8 weeks 50 °C/75% RH
Ranitidine tablet A	11.1 ± 1.0	300.3 ± 5.1	155.3 ± 0.7
Ranitidine tablet B	25.9 ± 0.6	186.3 ± 10.8	177.7 ± 2.0
Ranitidine reagent A	9.2 ± 1.3	16.0 ± 1.4	42.2 ± 1.4
Ranitidine reagent B	25.4 ± 0.9	58.5*	117.9*

Each result represents the mean ± S.D. ($n = 3$), *$n = 1$

studies were used in the storage study. The NDMA level in ranitidine tablet A was below the acceptable limit (0.32 ppm) on day 0, but increased to 1.42 and 116 ppm after 4 and 8 weeks, respectively, when stored at 40 °C/75% RH (Fig. 3a). In addition, more NDMA was produced under storage conditions of 50 °C/75% RH and exceeded 500 ppm after 8 weeks. Ranitidine tablet B contained a higher amount of NDMA (2.89 ppm) at the beginning of the study than tablet A. However, the level of NDMA generated from tablet B after 8 weeks storage at 40 and 50 °C was less than that from tablet A (Fig. 3a). Storage of the two ranitidine reagent powders at 40 and 50 °C for 8 weeks induced the production of smaller and different amounts of NDMA (Fig. 3b). We also observed browning of the ranitidine tablets and reagent powders after 8 weeks of storage at 40–50 °C (data not shown).

The formation of NDMA at levels above the official limit even in the samples stored for 4 or 8 weeks under the ICH-recommended accelerated stability testing conditions clearly indicates the risk of its formation during storage of the products at ambient temperatures. The preliminary result of the storage study was shared by regulatory bodies. The FDA recently requested the removal of all ranitidine products from the market because of the increasing amounts of NDMA noted in some ranitidine products over time and when stored at temperatures higher than room temperature, which may result in consumer exposure to NDMA levels above acceptable limits.[26] These findings also indicate the relevance of the regulatory decisions to stop the distribution of ranitidine products.

Factors Affecting the Formation of NDMA Various factors including differences in storage conditions (*e.g.*, humidity, oxygen, and temperature), solid-state forms (*e.g.*, crystal form) and their physicochemical properties, and drug formulations (*e.g.*, excipients, impurities, residual water, tablet/powder form, and coatings), may affect NDMA formation. In order to clarify the impact of these potential factors, the effect of storage conditions (humidity and oxygen) on NDMA formation was studied by storing ranitidine reagent powder A in open/closed/vacuum vials at 60 °C/75% RH for 1 week. The amount of NDMA newly formed during storage in the vacuum vial, in which the air has been removed and hermetically sealed with a lid to prevent moisture/oxygen infiltration, was much less than that in the closed and open vials (Fig. 4). These data suggest that the formation of NDMA in ranitidine is triggered by exposure to the atmosphere (*e.g.*, moisture and oxygen), as well as by high-temperature conditions. The variation in the rates of NDMA formation observed on storage of tablet A and B (Fig. 3a) can be partially explained by their different coatings and/or packaging, which determined the exposure to moisture and oxygen. For example, both tablets were film-coated, but different excipients were used.

Ranitidine HCl has been reported to exist in two crystalline forms, namely Form 1 and Form 2,[27] and differences in stability of polymorphic crystals may be another factor influencing NDMA formation. Hence, the crystal form of the samples was evaluated with X-ray diffraction (XRD) (Fig. S2). The XRD patterns of the reagent powder A and B indicated identical ranitidine crystalline form and that they are Form 2 (stable form) from the characteristic diffraction peak at near $2\theta = 20°$.[28] Therefore, the differences in the profiles of NDMA formation observed for reagents A and B (Fig. 3b) were not due to the difference in the crystal form but were attributable to other factors. Scanning electron microscopy observations suggested some differences in particle morphology between ranitidine reagent powder A and B (Fig. S3). Reagent A formed dense clumps with a diameter of approximately 300 μm, whereas sparse agglomeration was observed in reagent B. The relevance of the morphological differences on the NDMA formation should be intriguing topic for further study.

The amount of nitrite, which is considered one of the factors influencing NDMA formation,[19] in ranitidine used in this study was analyzed by ion chromatography. Table 2 clearly shows that the storage of each ranitidine tablet/reagent for 8 weeks under high-temperature conditions led to an increase in nitrite from Day 0. It suggested contribution of nitrite produced by the self-decomposition of ranitidine to the formation of NDMA in the ranitidine formulations, while clear relationship between the amounts of nitrite and NDMA was not observed.

Conclusion

In this study, we examined the effect of high-temperature storage of ranitidine on the formation of NDMA and then assessed factors affecting NDMA formation. The current findings clearly indicate that temperature-dependent formation of NDMA occurred during the storage of ranitidine tablets and reagent powders. Exposure of the atmosphere and nitrite produced by the self-decomposition of ranitidine may have contributed to NDMA formation during storage. Although it is not fully understood what/how the self-decomposing products

of ranitidine (including nitrite) contribute to the formation of NDMA in the chemical reaction, NDMA formation observed during the storage of ranitidine tablets necessitates the used of additional measures to control stability-related nitrosamine impurities in order to mitigate the safety risk of these products throughout their lifecycle. As many factors and complexities are involved in the generation of NDMA, further research is required to understand the process completely. Currently, we are performing an in-depth analysis of the mechanism of NDMA formation by focusing on the self-decomposition of ranitidine.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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