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Rapid Communication

Ranitidine: A Proposed Mechanistic Rationale for NDMA Formation and a Potential Control Strategy

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ABSTRACT

The formation of N-nitrosodimethylamine (NDMA) in ranitidine hydrochloride drug substance (DS) and drug products has attracted considerable attention over the last few years. The drug structure is unusual in that it contains a vinyl nitro moiety. Although a variety of studies have been carried out to understand how NDMA is formed in the DS solids, a mechanistic description of NDMA formation has remained elusive. A new mechanistic view of NDMA formation is detailed here. Autoxidation of ranitidine can rationalize nitrite ion and dimethylamine liberation from ranitidine. The subsequent nitrosation is argued to be due to conversion of nitrite ion to the gas phase nitrosating agent nitrosyl chloride, NOCl. Oxygen scavenging packaging systems should be able to stop the autoxidation, and thus shut down the nitrite release from ranitidine. Without nitrite release NDMA cannot form. This may provide a practical means to stabilize ranitidine DS and solid dosage formulations against NDMA formation.

Introduction

The discovery of the nitrosamine N-nitrosodimethylamine (NDMA), in valsartan drug substance (DS) in 2018 drove subsequent efforts to understand how NDMA could form during DS manufacturing processes. The FDA became comfortable that NDMA formation, in the sartan family case, was limited to the DS manufacturing process. In 2019, the FDA was alerted[1] to elevated levels of NDMA in ranitidine (see Fig. 1 for ranitidine and NDMA structures). As the investigation proceeded, it became clear that NDMA levels in ranitidine DS and drug products could be elevated post-manufacture by increased storage temperatures.[1,2] This brought into question NDMA growth potential during shipping, and concerns about growth during the two-year shelf life. Part of that concern was that there was not a mechanistic understanding as to how NDMA growth in ranitidine could occur post-manufacture to better judge risk and plan mitigation. No such understanding was found or has yet been offered.[3-7] The FDA thus requested recalls of all ranitidine products from the market in April, 2020. There remains clinical desire for ranitidine use[1], and we suspect a similar view among some of the former over the counter consumers of Zantac.

Numerous studies have shown that ranitidine HCl DS and drug products form NDMA when heated and exposed to moderate humidity.[2,4-7] Ranitidine is unusual in that is has a vinyl nitro moiety. The general current construct of NDMA formation in ranitidine HCl is depicted in Fig. 1. The ranitidine drug substance is viewed to be the source of both dimethylamine (DMA) as well as nitrite ion. That pathway is unknown and represented by process (1) in Fig. 1. Once nitrite is produced, it must be transformed into a nitrosating agent. Generally, converting nitrite into a nitrosating agent is well known in the context of (nitrite) being in a dilute solution of nitrous acid[8,9] at pH values $\sim<5$. The details of that nitrite conversion process then, in the case of ranitidine DS in the solid state are thus also unknown, and indicted by process (2) in Fig. 1. This note is to convey our mechanistic views of process (1) and (2) in Fig. 1, and to communicate the practical mitigation strategy against NDMA formation that is implied from them.

Discussion

Summary of Key Points of the Work by King et al

The most comprehensive study of NDMA generation from ranitidine HCl DS and drug product was carried out by King et al.[4] The authors studied the known ranitidine degradation pathways and could not account for how either the vinyl nitro moiety or the dimethylamine moiety could be lost. Through a labeling experiment, they

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even explored the possibility of an intramolecular reaction of these two groups. The data clearly ruled out the intramolecular reaction, and proved that the nitro moiety of one molecule was ultimately reacting with the dimethylamine moiety of a different ranitidine molecule. Other experiments discounted the role of impurities. A large survey of NDMA levels in DS and drug products showed a slow NDMA growth with age, but considerable variability within the data set (this data set is examined in more detail below). Another important finding was there was two different crystal morphologies found. One morphology had a much higher proclivity to form NDMA (that morphology we will call the "problematic morphology" henceforth), than the other case which King et al. refer to as the columnar morphology. It was noted the morphologies have different surface properties. Solid state NMR was carried out to determine that each morphology adsorbed very different amounts of the isolation solvents IPA and methanol (as well as water) onto their crystalline surfaces (the solvents and water were not distributed throughout the crystal lattice). These two morphologies will be discussed further in a subsequent section. No reaction mechanism was suggested describing how DMA or the nitrite ion could be cleaved from ranitidine, or for how the new N-NO bond formation occurs to create NDMA.

A Chemical Rationale for DMA and Nitrite ion Formation from Ranitidine: Autoxidation

In considering Fig. 1, our familiarity with oxidation processes[10-12] provided us the realization that both DMA and the nitrite ion could be liberated from ranitidine by autoxidation of ranitidine; that is, by the reaction (and propagation) of ranitidine peroxyl radicals with ranitidine itself. Two major peroxyl radical pathways would operate in our view (peroxyl radical reactions have been reviewed [13,14]). The first is shown in Fig. 2 and leads to the formation of the hemiaminal, which readily rearranges to release DMA and leaving ranitidine aldehyde 1 (the ranitidine hydroperoxide also forms, which drives EP impurity E, the N-oxide on the dimethyl amine N atom). The reversible dehydration of the hemiaminal to the iminium species is also shown. Fig. 3 shows the other major reaction pathway of the same peroxyl radical; in this case an addition reaction to the (non-conjugated) C=C double bond system bound to the nitrite group. In Fig. 3, we show the well-known case in which an epoxide forms across the C-C bond after the initial peroxyl radical addition.[13,14] The epoxide in

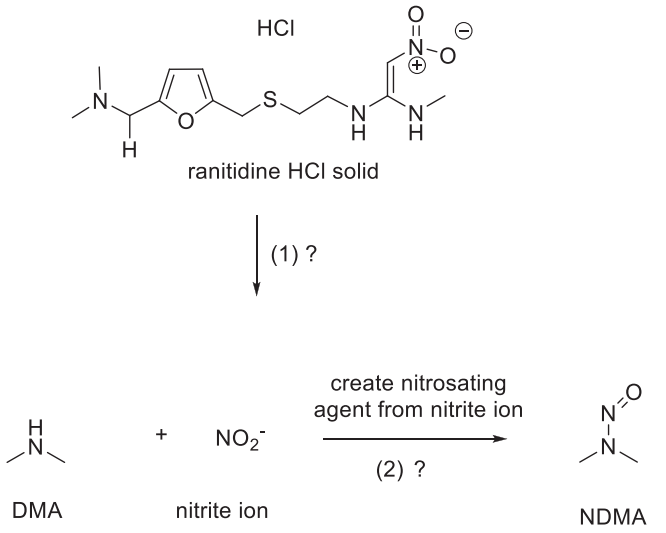

Figure 1. Current construct of NDMA formation mechanism in ranitidine HCl solids. Processes (1) and (2) are not known.

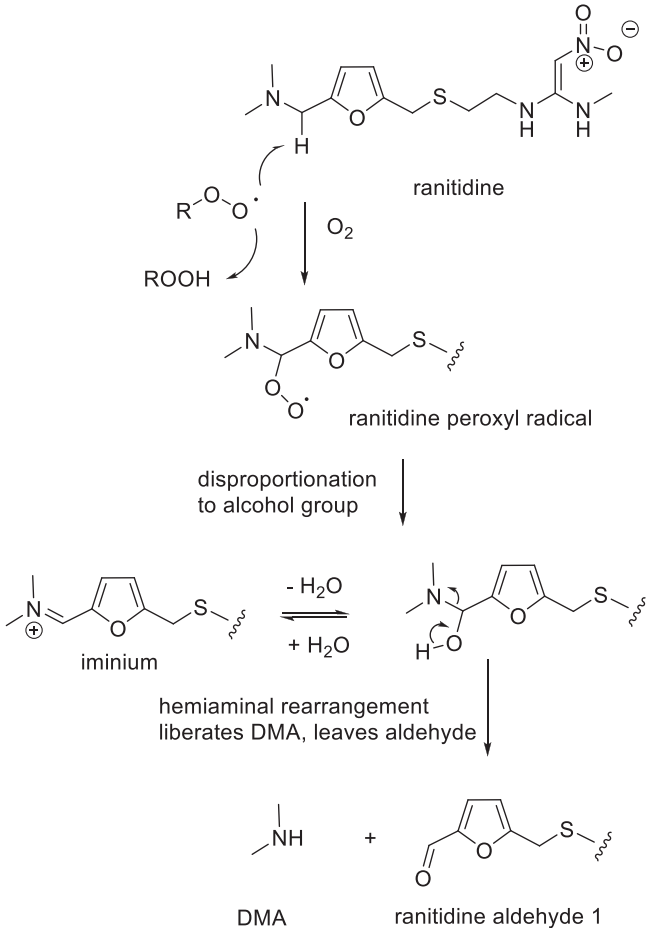

Figure 2. Autoxidation of ranitidine yielding DMA and ranitidine aldehyde 1. Note the ROOH (hydroperoxide) formed can react with Ranitidine to give the EP impurity E (N-oxide) and another ranitidine hemiaminal. Note consumption of oxygen.

Fig. 3 is proposed to undergo a rearrangement facilitated by either of the two amine N-H bonds to form another ranitidine aldehyde, while simultaneously liberating the nitrite ion. The displacement of nitrite from alpha-nitro epoxides has been noted.[15] Fig. 3 also shows the expected generation of the ranitidine alkoxyl radical, which drives more peroxyl radical formation and ends as the hemiaminal in Fig. 2.

The peroxyl radical reactions in Figs. 2 and 3 are consistent with the intermolecular reaction found by King et. al; the nitrite and DMA are from different molecules. The autoxidation we describe here (Figs. 2 and 3) would be occurring primarily on the crystal surface regions of the ranitidine DS. King et al. studied ranitidine DS solids in the 50°C-80°C temperature range at 10-30% relative humidity (RH). Their results indicate a ~2-3-fold increase in NDMA formation rate for each 10°C, and imply a ~2-fold increase in NDMA formation rate in going from 10% RH to 30% RH. These values, from our perspective, are generally consistent with a degradation process such as autoxidation. It is instructive to further consider the DS particle surface conditions. Residual solvent analysis of the problematic morphology showed there was 0.28% w/w IPA and 0.20% w/w methanol on the DS particle surfaces, and at 70% RH there was also 0.063% w/w water adsorbed (total 0.54% adsorbed solvents). Using the specific surface area of the problematic morphology of 0.24 m^2/g, and assuming solvent and particle densities of unity, then the adsorbed solvents can be calculated as a micro-layer about 200 angstroms thick [1 gram DS has volume 1 cm^3 or $10^{24}Å^3$, 0.54% adsorbed solvents thus have a

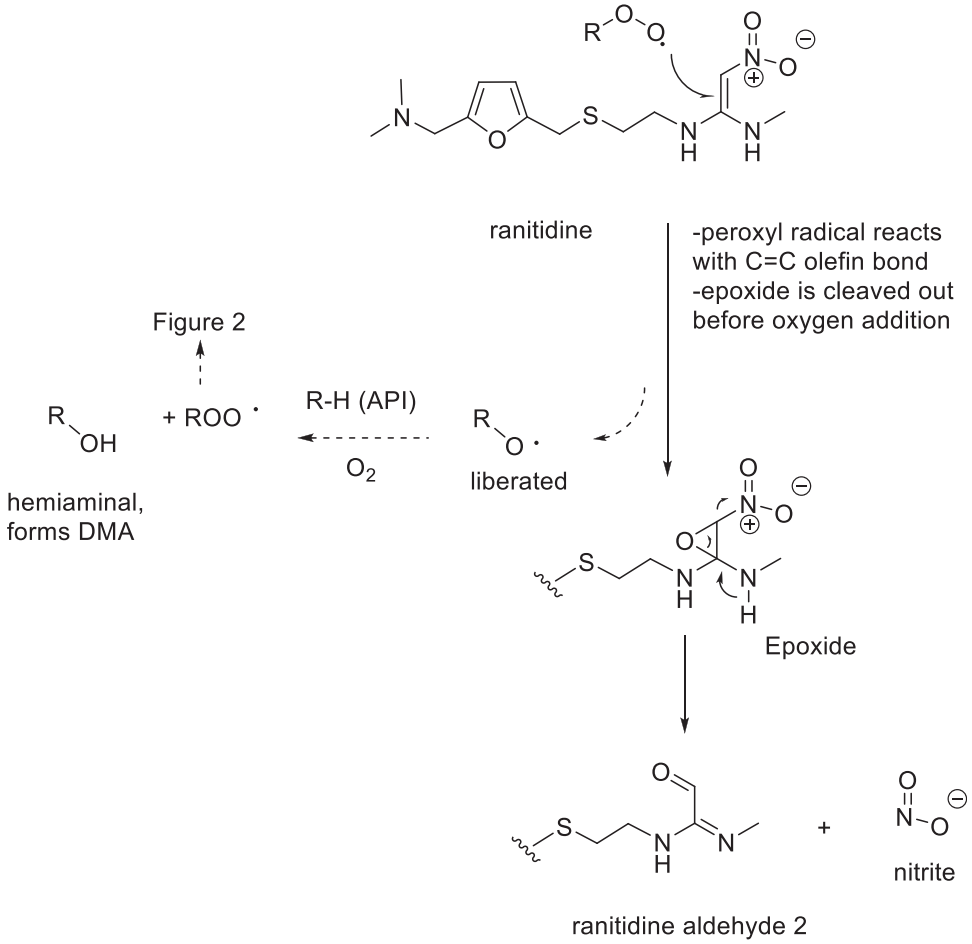

Figure 3. Reaction of peroxyl radical with the C=C olefin bond of ranitidine. Shown is olefin epoxidation. Either amine N-H bond can facilitate the epoxide rearrangement to an aldehyde with liberation of nitrite; we show the N-methyl amine case above. Note consumption of oxygen.

volume of 0.0054×10^{24}Å^3 = 5.2×10^{21} Å^3. The adsorbed solvent volume divided by the DS specific surface area/g is then the thickness of the micro-layers; (5.2×10^{21} Å^3 /0.24×10^{20} Å^2) ≈ 200 Å]. These micro-layers would be saturated with ranitidine HCl, and could provide the medium for the peroxyl radical reactions/propagation (Figs. 2 and 3). The amount of amorphous/dissolved ranitidine associated with these micro-layers would be very large with respect to the 1-20 ppm NDMA being formed, but below the % amorphous material that might be detectable by XRPD.

Transforming the Nitrite into a Nitrosating Agent: Nitrosyl Chloride Formation in Adsorbed Solvent Micro-Layers on Ranitidine Drug Particle Surfaces

Our study of the King et al. data leads us to conclude that the nitrite released by peroxyl radical reaction (Fig. 3) is converted into the nitrosating agent nitrosyl chloride, NOCl, in the adsorbed solvent micro-layers of the ranitidine HCl solids. Ranitidine HCl is freely soluble in water, soluble in methanol at ~250 mg/ml, and in IPA at ~1 mg/ml.[16] Consider that in water, the pH of a 13 mg/ml solution of ranitidine HCl is pH 6.2, but at 130 mg/ml, the measured pH is 5.0.[7] The solubility provided by the (~50% IPA/~40% methanol/~10% water) micro-layers of the problematic morphology DS we feel is likely high enough to similarly drive the "pH" down near pH 5 (~100 mg/ml). In these micro-layers the Cl ion content would be very high. Allowing a very dilute nitrite ion in the solvent layers to protonate to nitrous acid, HNO_2, consider Eq. (1) for the formation of NOCl in water[8]:

$$HNO_2 + Cl^- + H^+ \rightleftharpoons NOCl + H_2O \qquad K_{NOCl} = 1.1 \times 10^{-3} M^{-2} \text{ in water} \tag{1}$$

The low (10%) water content, high alcohol content, and high Cl ion content of the problematic morphology micro-layer would each favor formation of nitrosyl chloride (NOCl). NOCl is well known to act as a nitrosating agent, being able to readily react with neutral amines to form the new amine N-NO bond.[8, 9]

Given the equilibrium constant in water of only 1.1×10^{-3} M^{-2},[8] NOCl formation yields would be sensitive to the % water present. While the columnar morphology adsorbs slightly less water (0.043% at 70% RH as compared to 0.063%), King et al. found it adsorbs ~20-fold less alcohols on its surfaces (<0.01% IPA and 0.02% methanol). This yields a micro-layer composition containing about 60% water. This 6-fold higher water level will significantly limit the NOCl yields in Eq. (1) compared to the problematic morphology. The micro-layers of the columnar material are also ~10-fold less in "volume" which could lower the total nitrite ion liberated by peroxyl radical reactions (Fig. 3), thus further lowering NOCl yields. Overall, these two differences in micro-layer composition/volume could account for the much larger NDMA yields from the problematic morphology as compared to the columnar material. Finally, we highlight here that in the case of NOCl as the nitrosating agent, the initial liberation of DMA

(Fig. 2) might not even be required, as the DMA moiety may be able to undergo rapid nitrosative dealkylation due to the electron rich furan ring.[9]

Consideration of NDMA Levels in Ranitidine DS and Solid Oral Dosage Forms: Gas Volume- to-Drug Solids Ratio Effects from Gas Phase Nitrosating Agent NOCl

The data in the right hand column of Table 1 are adapted from the data provided by King et al.[4] and show NDMA ranges measured for numerous batches of ranitidine HCl DS (top line) as well as for two tablet formulations (note Table 1 also shows two solution formulations, these are viewed as having a different nitrosation mechanism and will be discussed briefly below). King et al. noted significant variation even within similar data sets, as well as the drop-off in upper NDMA levels when moving from DS (20 ppm in Table 1) to film coated tablets (8 ppm), and even further to 2 ppm in effervescent tablets. It was also noted that the NDMA levels in a given DS lot were typically higher than the same lot in drug products, suggesting that NDMA formation slowed down upon formulation. All of these observations and the data in Table 1 are consistent with the fact that the nitrosating agent NOCl is a gas at STP, in our view. The NOCl formed in ranitidine DS micro-layers will quickly get into the gas phase and establish an equilibrium over (throughout) the DS solids and the volume they are contained in. The nitrosation rate (either of DMA or the DMA moiety) will be proportional to the gas phase NOCl concentration within the DS solids volume.

A simple example is worthwhile working through to appreciate the resulting impacts on NMDA levels measured in various solids. Assume ranitidine HCl and any pharmaceutical solid excipient occupy 75% of the volume they are contained in (thus leaving 25% of their bulk volume available to NOCl gas), and all have bulk densities near 0.4 g/cm^3. Taking a glass container of any size and filling it with ranitidine HCl solids (capping it with an impermeable top) will give a gas volume-to-drug solids ratio of 0.625 cc/g [taking a 10-cc container, filled would be 4 g of ranitidine DS with a total of 2.5 cc volume between DS particles, giving a gas volume-to-drug solids ratio of 2.5 cc/4 g = 0.625 cc/g]. However, the same container only 50% filled with ranitidine HCl will have a gas volume-to-drug solids ratio of 3.1 cc/g; 5-fold higher [taking a 10-cc container, 50% full would be a total of (5 cc + (0.25 × 5cc))= 6.25 cc gas volume, with 2 g DS = 6.25 cc/ 2 g = 3.1 cc/g]. Thus, NDMA levels for the same lot of ranitidine HCl would trend over the longer term 5-fold lower in the 50% filled case, as compared to the full glass container. Formulation of a tablet in this analogy is taking the glass container and filling it (for example) one-half full of ranitidine HCl, and then filling the container the rest of the way with pharmaceutical excipients (i.e., a 50% drug loading example). This gives a gas volume-to-drug solids ratio of 1.25, 2-fold higher than the pure DS filled in the container (Table 1, center column). In this way, significant DS batch variation in NDMA values can occur depending on the nuances of the DS storage container/closure system that was sampled; as well as the history of how many times the particular storage container may have been opened transiently to atmosphere. Tablets will always have lower NDMA values than the DS used to make them.

Thus, in our view, in Table 1 the drop-off in upper NDMA range from around 20 ppm for DS to 8 ppm in film coated tablets reflects the ~40-50% drug loading in the 150 and 300 mg ranitidine HCl film coated tablets. This presumes that the "average" DS configuration has minimized headspace (like double polybag inside a drum), and that both the polybag and the film coating of the tablet provide enough resistance to NOCl diffusion to define an outer boundary. In the case of the effervescent tablets, there is another ca. 4-fold drop-off in NDMA levels from the film coated tablets (Table 1). We attribute this to the fact that these tablets are not film coated, so that they can rapidly dissolve. Each tablet is contained in a protective pouch with a significantly larger volume than the tablet itself (we estimate 2-3-fold larger, but do not have detailed information). Even if a two-fold larger pouch volume is assumed, along with a 50% drug load in the effervescent tablet, this gives a gas volume-to-drug solids ratio of 5.6 cc/g which is 9-fold larger than the DS case (Table 1, center column). Table 1 shows a 10-fold drop-off in upper NDMA bounds from the DS to effervescent tablet case, in excellent overall agreement. In this scenario, formulation of any DS batch will immediately reduce NMDA formation rates because of the increased gas volume-to-drug solids ratio in tablets.

The two solution formulations of ranitidine HCl shown in the lower portion of Table 1 are homogenous solutions with pH values near 7.0. While we view the peroxyl radical reactions as still occurring in the two solution cases, the acidic route of nitrosation in Eq. (1) is not plausibly operational. In these pH 7.0 liquid formulations it is proposed that nitrosation is accomplished by the aldehyde catalyzed nitrosation pathway originally demonstrated by Keeper and Roller.[17] Briefly, formaldehyde reaction with a secondary amine produces an iminium ion, with which nitrite ion can directly react to form the new N-NO bond (a detailed discussion of that mechanism here is beyond the scope of this work). The aldehyde catalyzed pathway has been recently examined in the context of pharmaceutical drug products.[18] In the ranitidine IV and oral solution cases, the catalytic aldehyde(s) are ranitidine based (formed in Figs. 2 and 3), although we note that the ranitidine aldehyde in Fig. 2 contains the strongly electron donating furan ring which would likely eliminate its ability to catalyze the nitrosation.[17,19] It should be noted that aldehyde catalysis is not thought to play a major role in the case of ranitidine DS or solid dosage forms. The aldehyde route would be a solution phase nitrosation (occurring on the ranitidine aldehyde in Fig. 3 in the micro-solvent layers). This is not consistent with the NDMA upper range values in Table 1 which support a gas phase nitrosating agent in the solid dosage forms (discussed above). The pH of the micro-solvent layers would also appear lower than the optimal pH value for the aldehyde catalyzed pathway (~pH 7).[17]

A simple Mitigation Strategy- Oxygen Scavenging Packing Technology?

This manuscript does not offer any new data on NDMA formation in ranitidine HCl DS and drug products. However, it does offer the first plausible mechanistic rationale for both the liberation of nitrite ion and DMA from ranitidine, as well as for the mechanism of the nitrosation reaction. As such, it provides numerous predictions against which experiments can be designed to refute or validate the proposed mechanistic pathways. Experiments might be designed to look for the evidence of the epoxide (Fig. 3), although the levels that might be expected would present a challenge. A more tractable experiment would be to take a known problematic lot of ranitidine DS and put different amounts of the DS solid into the same well defined container system (from filled to only 10% full, for example. This would give very different gas volume- to-drug solids ratios (as in Table 1). New NDMA formation rates should be very different in each

Table 1
NDMA levels from King et al.[4] DS and film coated tablets; batches tested is over 100 for top two lines, and over 30 batches of effervescent tablets.

Sample	Relative gas volume-to-drug solids ratio	NDMA range*,Ref. 4
Ranitidine HCl DS	1	0.1-20
Film coated tablets	2	0.2-8
Effervescent tablets	9	0.5-2
Oral solution	N/A, solution; pH = 7.0	0.7-3
IV solution	N/A, solution; pH = 7.0	0.2-1

* ppm relative to ranitidine free base. N/A not applicable

sample, being inversely related to the gas volume-to-drug solids ratio in each sample.

One of the most obvious and straightforward experiments would be to determine if oxygen scavenging packaging systems[20] can stabilize ranitidine HCl DS and drug products. Central to the proposed mechanisms here is the peroxyl radical reactions (Figs. 2 and 3) that release the nitrite (and DMA if required). These reactions require molecular oxygen. Without these reactions, NMDA will not form in the current mechanistic framework. Thus, oxygen scavenging offers a simple proof of mechanism, and could provide a tractable NDMA mitigation and control strategy in ranitidine HCl DS and drug products.

Other mitigation strategies could be considered. Using typical peroxyl radical scavengers such as butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA) to inhibit the peroxyl radical reactions in Figs. 2 and 3 could be difficult given the very small oxidation rates, which lead only to NDMA levels of tens of ppm over several years. If gas phase NOCl is presumed to be the nitrosating agent here, an ideal inhibitor would have presence in the vapor phase and be able to encounter NOCl and reduce it to non-nitrosating nitric oxide. In this regard, BHT and BHA are considered ineffective at blocking nitrosamine formation, while α-Tocopherol does show inhibitive properties.[21] However, these observations are in the context of N_2O_3 as the nitrosating agent, not NOCl. Nanda et al.[22] examined ascorbic acid, ascorbate, ferulic and caffeic acid, and α-Tocopherol in terms of their ability to inhibit nitrosation of a secondary amine (the nitrite ion was present in the excipients as an impurity). Significant inhibition was found at 1% (wt./wt.) inhibitors in the tablet. The nitrosation agent was not specifically investigated, making a direct comparison to the present gas phase NOCl case difficult. It would appear further experimental work is needed to clarify what inhibitors might act best against a nitrosating agent created in Eq. (1) and residing primarily in the gas phase.

A final thought around mitigation would be to consider if the situation would be any better off if chloride ion was not the DS counterion. Taking a phosphate salt as an example (letting all else be identical) the adsorbed solvent micro-layers would still acidify. Eq. (1) would be replaced by the general protonation of nitrous acid, in which case $H_2NO_2^+$ could be considered the nitrosating agent.[8] This would appear to force the nitrosating agent to exist in the solvent micro-layers, rather than the gas phase. This would be a significant difference compared to the suggested present case. However, only experimental data can provide a clue as to what the overall impact on NDMA formation rates would be.

Summary and Conclusions

In the unusual case of ranitidine HCl, we have proposed that NDMA formation is enabled by peroxyl radical epoxidation of the C=C double bond system bound to the nitrite group (Fig. 3). The epoxide is hypothesized to rearrange to release the nitrite ion. The liberated nitrite ion is converted to the nitrosating agent NOCl in the adsorbed solvent micro-layers on DS particle surfaces. The two different DS morphologies described by King et al. differ significantly in the percentage water in and the volume of their adsorbed solvent layers. This results in very different NOCl yields mediated through Eq. (1). Gas phase NOCl reacts with either DMA (Fig. 2) or the DMA moiety to form NMDA. A gas phase nitrosating agent can explain a number of curious observations made by King et al. with regard to variability and changes of upper NDMA levels found after DS is formulated. Without oxygen, the autoxidation in Figs. 2 and 3 cannot proceed, and nitrite ion (as well as DMA, if required) cannot be released from ranitidine. While further investigations to verify the mechanisms proposed here should be carried out, the use of oxygen scavenging packaging systems should be investigated immediately. The success of such oxygen removal systems would support the mechanisms proposed here, and a provide a practical control strategy against NDMA formation in ranitidine HCl DS and solid oral dosage forms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. see, for example chronology of events Wagner JA, Dinh JC, Lightdale JR, Gold BD, Colombo JM. Is this the end for ranitidine? NDMA presence continues to confound. *Clin Transl Sci*. 2021;14:1197–1200.
2. Najafi RR. Re: Emery Pharma citizen petition. Emery Pharma. 2020. https://emerypharma.com/wp-content/uploads/2020/01/EP-Ranitidine-FDA-Citizen-Petition-v21-January-2-2020.pdf.
3. Aldawsari FS, Alshehri YM, Alghamdi TS. N-nitrosodimethylamine (NDMA) contamination of ranitidine products: a review of recent findings. *J Food Drug Anal*. 2021;29:39–45.
4. King FJ, Searle AD, Urquhart MW. Ranitidine-investigations into the root cause for the presence of NNitrosoN,ndimethylamine in ranitidine hydrochloride drug substances and associated drug products. *Org Process Res Dev*. 2020;24:2915–2926.
5. Yokoo H, Yamamoto E, Masada S, Uchiyama N, Tsuji G, Hakamatsuka T, Demizu Y, Izutsu KI, N-Nitrosodimethylamine Goda Y. (NDMA) formation from ranitidine impurities: possible root causes of the presence of NDMA in ranitidine hydrochloride. *Chem Pharm Bull*. 2021;69:872–876.
6. Abe Y, Yamamoto E, Yoshida H, Usui A, Tomita N, Kanno H, Masada S, Yokoo H, Tsuji G, Uchiyama N, Hakamatsuka T, Demizu Y, Izutsu KI, Goda Y, Okuda H. Temperature-dependent formation of N-nitrodimethyl amine during the storage of ranitidine reagent powders and tablets. *Chem Pharm Bull*. 2020;68:1008–1012.
7. Teraoka R, Otsuka M, Matsuda Y. Effects of temperature and humidity on the solid-state chemical stability of ranitidine hydrochloride. *J Pharm Sci*. 1993;82(6):601–604.
8. Ashworth IW, Dirat O, Teasdale A, Whiting M. Potential for the formation of N-nitrosamines during the manufacture of active pharmaceutical ingredients: an assessment of the risk posed by trace nitrite in water. *Org Process Res Dev*. 2020;24:1629–1646.
9. Lopez-Rodríguez R, McManus JA, Murphy NS, Ott MA, Burn MJ. Pathways for NNitroso compound formation: secondary amines and beyond. *Org Process Res Dev*. 2020;24:1558–1585.
10. Harmon PA, Boccardi G. Oxidative susceptibility testing. In: Baertschi SW, Alsante K, Reed RA, eds. *Pharmaceutical Stress Testing – Predicting Drug Degradation*. 2nd edition. London: Informa Healthcare; 2011:168–191.
11. Harmon PA, Kosuda K, Nelson E, Mowery M, Reed R. A novel peroxy radical based oxidative stressing system for predicting oxidative instability of active pharmaceutical ingredients. *J Pharm Sci*. 2006;95(9):2014–2028.
12. Harmon PA, Biffar S, Pitzenberger SM, Reed RA. Mechanism of the solution oxidation of rofecoxib under alkaline conditions. *Pharm Res*. 2005;22(10):1716–1726.
13. Ingold KU. Peroxy radicals. *Acc Chem Res*. 1969;2:1–9.
14. Sheldon RA, Kochi JK. Metal catalyzed oxidations of organic compounds in the liquid phase: a mechanistic approach. In: Elay DD, ed. *Advances in Catalysis*. New York: Academic Press; 1976:274–413.
15. Vankar YD, Shah K, Bawa A, Singh SP. Chemistry of α-nitroepoxides: synthesis of useful intermediates via nucleophilic ring opening of α-nitroepoxides. *Tetrahedron*. 1991;47(22):8883–8906.
16. Trifkovic M, Rohani S. Polymorphic generation through solvent selection: ranitidine hydrochloride. *Org Process Res Dev*. 2007;11:138–143.
17. Keeper LK, Roller PP. N-nitrosation by nitrite ion in neutral and basic medium. *Science*. 1973;181:1245–1247.
18. Harmon PA. Trace aldehydes in solid dosage forms as catalysts for nitrosating secondary amines. *J Pharm Sci*. Published online. https://doi.org/10.1016/j.xphs.2022.10.033.
19. Lv CL, Liu YD, Zhong RG. Theoretical investigation of N-nitrosodimethylamine formation from dimethylamine nitrosation catalyzed by carbonyl compounds. *J Phys Chem*. 2009;113(A):713–718.
20. Many different oxygen scavenging systems are available, see for example https://www.multisorb.com/oxygen-absorbers/.
21. Mergens WJ, Newmark HL, et al. Antioxidants as blocking agents against nitrosamine formation. In: Simic, et al., ed. *Autooxidation in Food and Biological Systems*. New York: Springer Science+Business Media; 1980:387–403.
22. Nanda KK, Tignor S, Clancy J, Marota MJ, Allain LR, D'Addio SM. Inhibition of N-nitrosamine formation in drug products: a model study. *J Pharm Sci*. 2021;110:3773–3775.