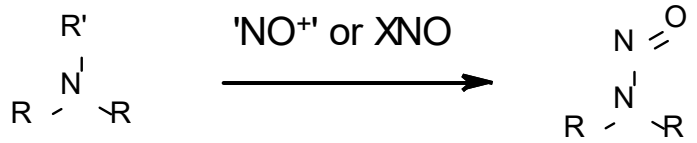
NDMA and Beyond: A Biased Kinetic Model to Assess Nitrosation Risk in Solid Drug Products

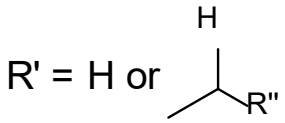
Ian Ashworth

Chemical Development, Pharmaceutical Technology & Development, Operations, AstraZeneca

May 2024

Introduction: Nitrosamine Formation





$X = NO_2^-, NO_3^-, Cl^-, Br^-, NCS^-, AcO^-, H_2O$ etc

- The conditions present in a solid drug product mean that amine nitrosation has the greatest relevance, so this will be my focus
  1. Nitrosating agents and amine nitrosation
  2. Nitrosation experiments to assess risk from complex structures
  3. Predictive aqueous solution model (kinetics)
  4. Nitrosation in the context of a drug product
  5. Using a biased predictive model to assess drug product risk
- Synthetically there are many ways of making nitrosamines not all of which start from amines

Williams, D. L. H. *'Nitrosation Reactions and the Chemistry of Nitric Oxide'* Elsevier, 2004

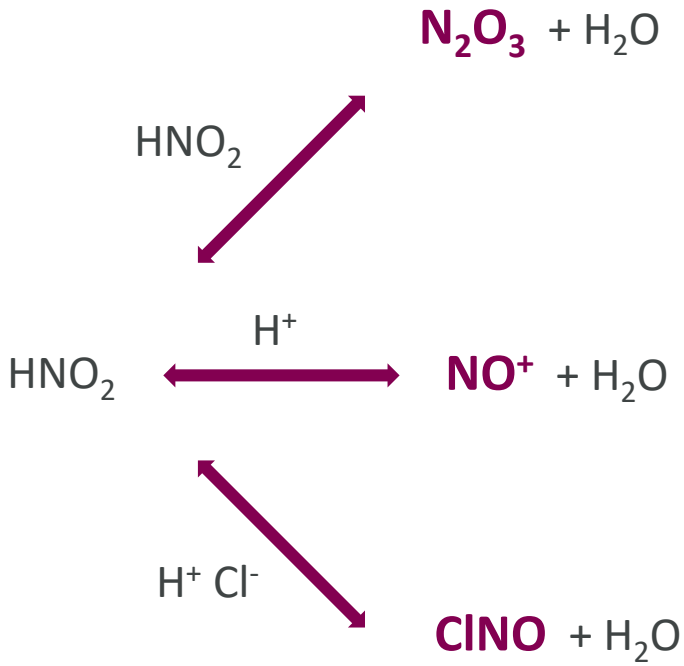
[2] Burns, M. J. *et al. Org. Process Res. Dev.*, **2020**, *24*, 1558.

Nitrosating Agents with Drug Product Relevance

Can be grouped into three groups:

1. Derived from nitrous acid / nitrite
   - Nitrous acid is not a nitrosating agent and needs to be transformed into a nitrosating agent (see right)
   - Nitrite can act as a nitrosating agent in aqueous solution via a formaldehyde catalysed pathway
2. Oxides of nitrogen (NOx)
   - N_2O_4 and N_2O_3 (trace) are components of NOx and are known to nitrosate amines in aqueous and organic solutions
3. Alkyl nitrites (RONO)
   - Alkyl nitrites will nitrosate amines in organic solvents and react directly with amines at high pH in aqueous solution

Nitrosating agents derived from HNO_2



All exhibit very high rate constants in their reactions with secondary amines

Williams, D. L. H. *'Nitrosation Reactions and the Chemistry of Nitric Oxide'* Elsevier, 2004, Chapter 1.

Ashworth, I. W. *et al. Org. Process Res. Dev.*, **2020**, *24*, 1629.

Nitrosation Experiments: Will a NDSRI form?

Most active pharmaceutical ingredients possess multiple structural features that could react with nitrosating agents.

- Which product will you form with trace nitrite?
- Is it a member of the Cohort of Concern?

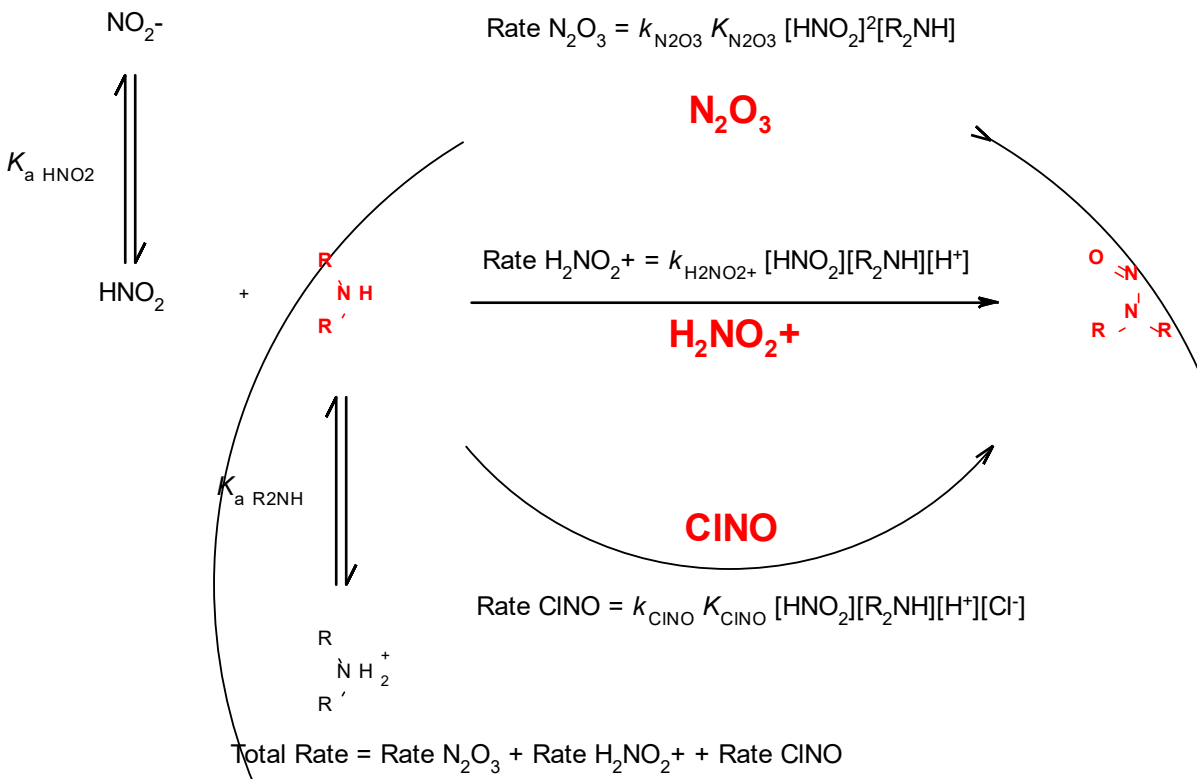
- Such questions can be answered by carefully conducted nitrosation experiments
  - Failure to form nitrosated products can de-risk a drug substance
  - Can be used to assess complex tertiary amines to see if they behave as activated trialkylamines
  - Formation and decomposition can suggest that the nitrosated product may not be stable – need to identify the final product
  - Nitrosated products formed may not be nitrosamines – need to characterise as they may still fall under ICH M7
  - In the event of multiple products - sub stoichiometric experiments can identify the product likely to form with trace nitrite

Blanazs, A. *et al. Org. Process Res. Dev.*, **2023**, *27*, 1784 – Suggested conditions for investigating NDSRI formation

Curran, T. *et al. Org. Process Res. Dev.*, **2023**, 27, 1714 – Discusses where risks exist for tertiary amines

Predicting Aqueous Amine Nitrosation (HNO_2 based)

A kinetic basis for a model



$$[R_2NNO]_t = Total\ Initial\ Rate \times t$$

Aqueous nitrous acid based nitrosation chemistry has been thoroughly studied from a kinetic point of view meaning that rate constants for many simple dialkylamines have been measured.

- Values change by less than a factor of 10 across a pK_a range of 5 to 11. Taken as evidence of an encounter-controlled process.
- Possible to calculate initial rates for nitrosation by N_2O_3, $H_2NO_2^+$, and ClNO (BrNO) from the published rate laws. A simple linear, zero order, very conservative, model can be implemented in Excel.
  - A full kinetic model requires the solution of the differential equations which may be achieved in any appropriate kinetic simulation package
- This model makes no allowance for the decomposition of nitrous acid via N_2O_3 to form nitric oxide (NO)

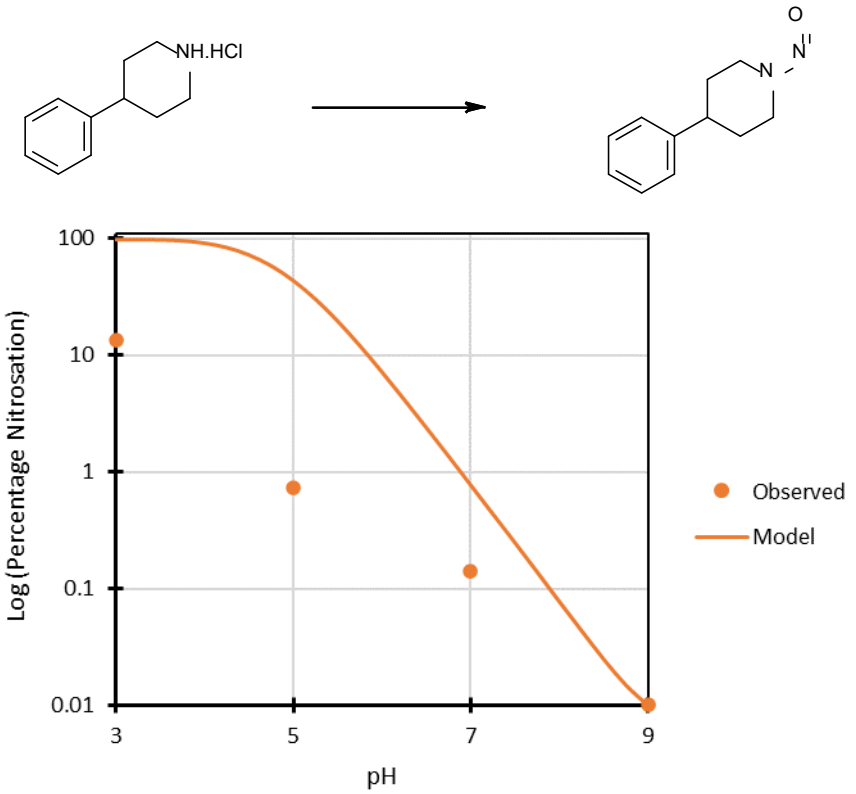
Ashworth I. W. *et al. Org. Process Res. Dev.* **2020**, *24*, 1629 - Trace nitrite in water and simple dialkylamine model

Ashworth I. W. *et al. Org. Process Res. Dev.* **2023**, *27*, 1759 – Limited model validation, extension to anilines and polybasic amines

Model Validation

- Validation experiments carried out using 4-phenyl piperidine as a test substrate
  - Excess nitrite at 25°C and 60°C
  - Model consistently overpredicts versus measured levels of nitrosamine formation
- Limited data generated for diethylamine under the same conditions at pH 3.
  - 2.3% conversion to NDEA observed at 25°C compared to a prediction of total nitrosation

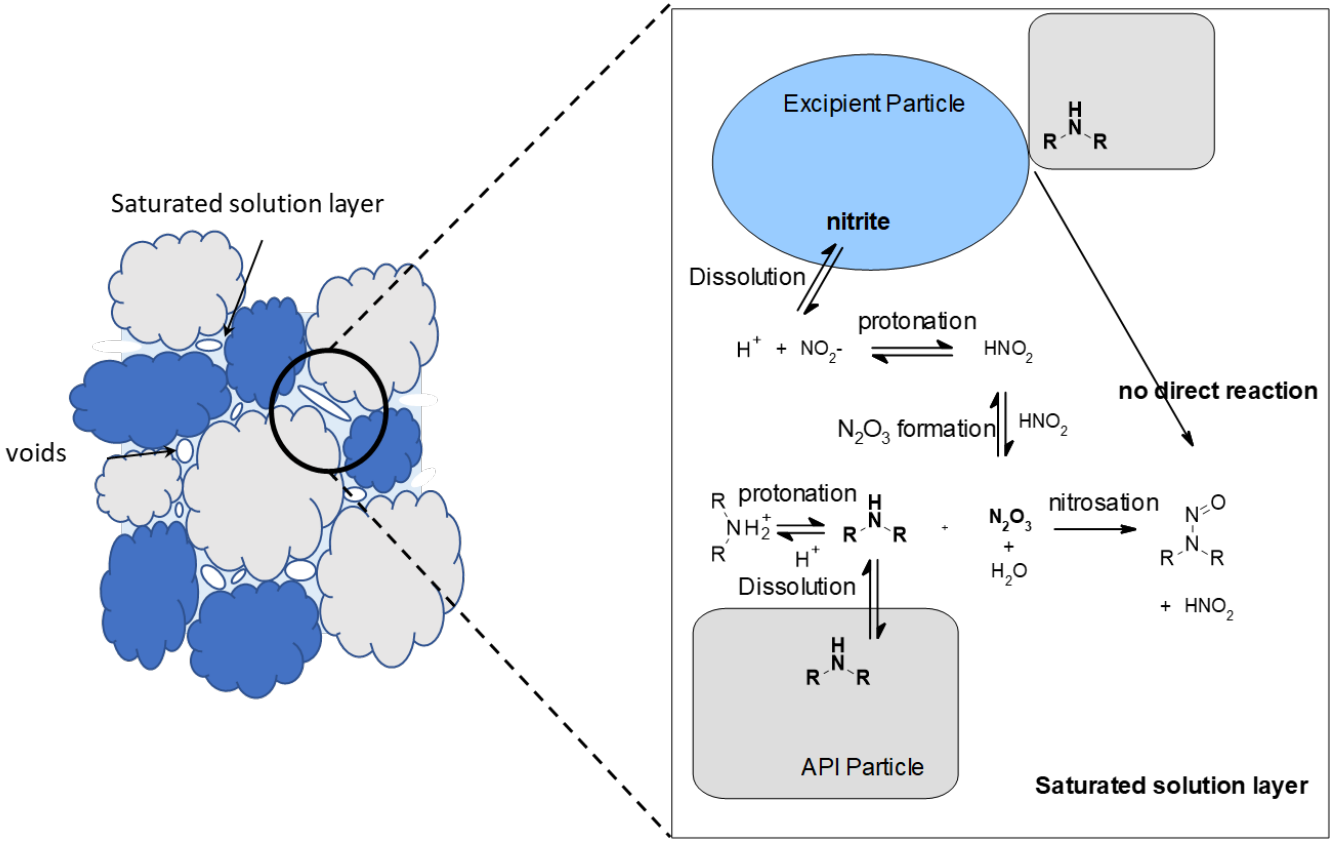
4-Phenyl piperidine nitrosation



[4-PP] = 0.1 M, [$NaNO_2$] =0.2 M, 24 hours at 25°C

Ashworth I. W. *et al. Org. Process Res. Dev.* **2023**, *27*, 1759 – Limited model validation, extension to anilines and polybasic amines

Nitrosation in a Solid Drug Product



Q: How does a multi-component reaction occur in a heterogeneous solid?

Hypothesis: reaction doesn't occur at the contacts between particles.

- Reaction occurs within a saturated solution layer present within the product that bridges the particles.
- This is an aqueous nitrosation problem!

Taylor, L. S. *et al. J. Pharm. Sci.*, **2010**, *99*, 3719 – Application of saturated solution layer concept to DS degradation

Moser, J. *et al. J. Pharm. Sci.*, **2023**, *112*, 1255-67 – Model product nitrosation experimental results

Applying a Saturated Solution Layer Model

Known Scenario Parameters

- Nitrite content of excipients from excipient database or analysis
  - Unlikely all will be available to react - **Assume all is available**
- Secondary amine content based on drug substance (DS) load and purity
  - API will usually be at its saturating solubility in the solution layer
  - Impurity amines may or may not be available – **Assume level that it's all available** and at the specification limit in the absence of data

Unknown Scenario Parameters

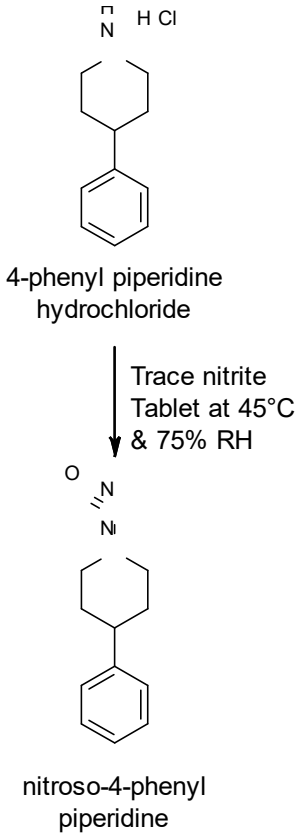
- Volume of solution phase in the product
  - Take the **lowest** measured water content in the packed product from stability studies allowing for bound water
- pH of the saturated solution layer – **really important!**
  - Measure the pH of a slurry of the relevant blend of materials in a low volume of water
  - pH of a saturated solution of the DS

Initial conditions chosen to maximise predicted rate of nitrosamine formation

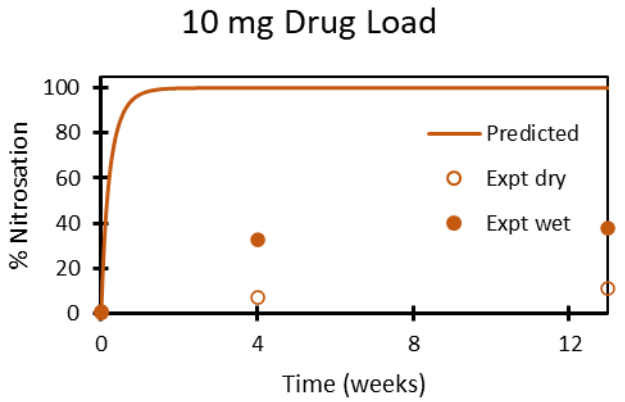
Boetzel, R. *et al. J. Pharm. Sci.*, **2023**, *112*, 1615 – Excipient nitrite database summary data and analytical methods

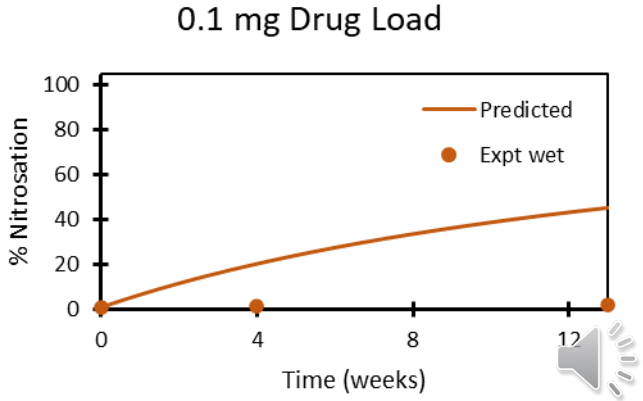
Validation 1: Application to a Model Drug Product: 4-Phenyl Piperidine Hydrochloride – 45°C / 75% RH

- Tablets prepared containing 10 mg and 0.1 mg 4PP HCl using a fairly typical excipient blend
  - Total tablet mass 100 mg
  - Native nitrite content in excipients 0.55-0.6 ppm
  - 6.0% free water in the tablet based on moisture sorption isotherm
  - pH 5 based on a saturated solution of 4PP HCl
  - Tablets prepared by wet granulation or dry blending



Predicted *versus* observed





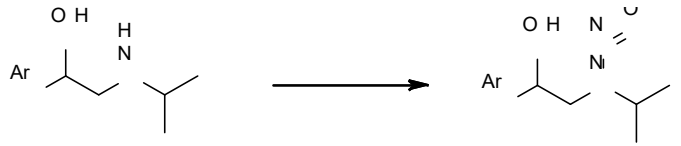
Moser, J. *et al. J. Pharm. Sci.*, **2023**, *112*, 1255-67 – Model product experimental results

Total consumption of the available nitrite would give 228 or 248 ng of nitroso-4-phenyl piperidine per tablet

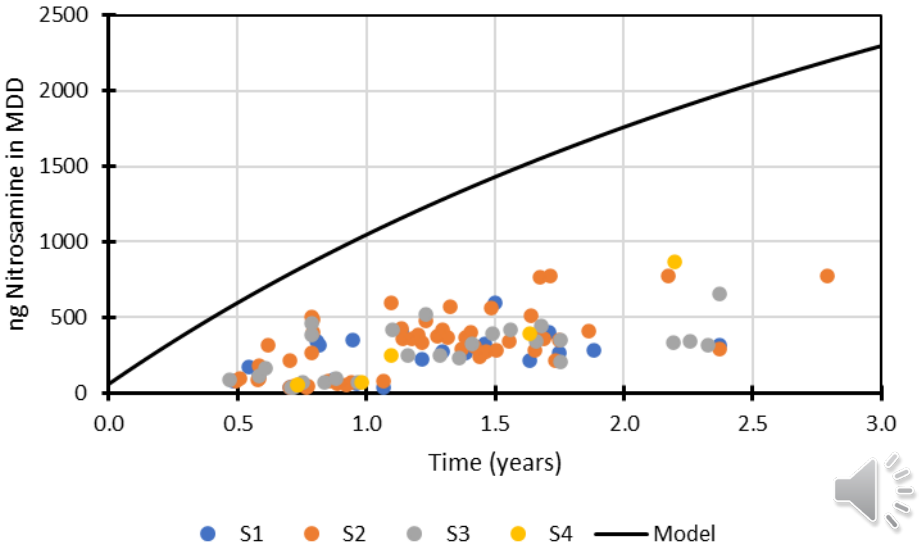
Kinetic simulations used Berkeley Madonna Version 8.3 with a 4th order Runge-Kutta approach to the solution of the differential equations

Validation 2: Application to a β-Blocker

- Four different dosage strengths of solid dosage form containing a salt of the drug substance.
  - Total reaction of the nitrite present in the excipients would form > 6000 ng of the NDSRI in the MDD.
  - Kinetic model predicts ~2300 ng in the MDD at the end of three years at 25°C, which is > the AI
  - Testing of retained samples and batches set down on stability showed NDSRI to be significantly < than the AI of 1500 ng/day
  - Diisopropylamine could be present as a DS impurity at trace levels – kinetic model gives < 1ng/day of NDIPA in the MDD



predicted *vs.* measured



Thank You! & Acknowledgements

AstraZeneca

- Heather Akehurst
- Alex Blanazs
- Gair Ford
- Mark Harrison
- Dawn Sievwright
- Andrew Teasdale
- Paula Tomlin

IQ Consortium Nitrosamine Working Group

- Tim Curran (Vertex)
- Olivier Dirat (Pfizer)
- Justin Moser (Merck & Co)
- Kausik Nanda (Merck & Co)
- Trevor Rainey (Gilead)
- Garry Scrivens (Pfizer)
- Mat Whiting (GSK)
- Mike Urquhart (GSK)

Future Research Directions

- Making use of product testing data in an anonymised manner to probe the availability of nitrite and amines dependent upon processing method, product type and amine level (trace impurity, related substance impurity or drug substance). Can the model be improved to reduce the testing burden while still being conservative?
- NOx can lead to nitrosamine formation. Limited studies are ongoing to probe drug product risk. Further work likely to be required to understand risks in commercial formulation equipment.