RESEARCH PAPER

Drug-Excipient Interaction Guided Design Of A Solid Dispersion System For Nitrosation Risk Reduction In Varenicline

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ABSTRACT
Nitrosamine impurities represent a major regulatory concern because of their carcinogenic potential and very low acceptable intake limits. Varenicline, an amine-containing drug substance used for smoking cessation therapy, is susceptible to nitrosation under acidic and/or moisture-rich conditions in the presence of trace nitrite, forming N-nitroso-varenicline. Here, we compare two mechanistically distinct, formulation-relevant mitigation concepts: (i) polymer-matrix shielding of the nitrosatable secondary amine within a hydroxyl-rich maltodextrin solid dispersion and (ii) a small-molecule interaction model using cysteine as a comparator. A varenicline–maltodextrin solid dispersion was prepared using rotavapor-assisted solvent evaporation to promote intimate molecular mixing while minimizing prolonged water exposure, followed by direct-compression tablet development using low-nitrite excipients and sodium citrate to maintain a microenvironmental pH > 6. AutoDock Vina was modified into a physicochemical association model (molecular docking), and used to determine drug-excipient interactions. The varenicline-maltodextrin complex which scored the highest had a positive docking affinity score of -2.66 kcal/mol and a hydrogen bond of 2.84 Å between the amine group of varenicline and the hydroxyl groups of maltodextrins. A similar docking score was obtained with cysteine (−2.65 kcal/mol) and hydrogen-bond formation (representative distance of approximately 2.55 Å), indicating the possibility of hydrogen-bond formation, but not polymeric encapsulation. In general, the synergistic interaction-based shielding, decreased solid dispersion mobility, pH regulation, and excipient nitrite reduction offer a logical, multilayer model proposed to reduce the risk of nitrosation in varenicline solid dosage forms.

Keywords: Varenicline; N-nitroso-varenicline; mitigation of nitrosamine; solid dispersion; maltodextrin; cysteine; molecular docking.

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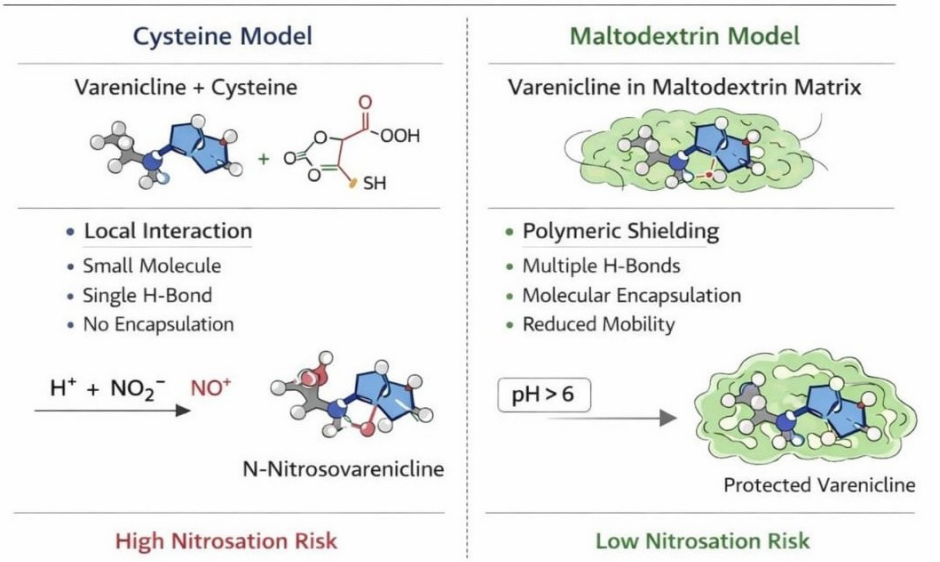
GRAPHICAL ABSTRACT



Mechanistic Comparison of Nitrosation Mitigation in Varenicline: Cysteine vs. Maltodextrin Matrix

1. INTRODUCTION

The presence of nitrosamine impurities has become a quality and regulatory concern in pharmaceutical products because of their carcinogenic nature and very low acceptable limits of intake of many nitrosamines (Tuesuwan and Vongsutilers, 2023; Akkaraju et al., 2023). This global challenge has prompted collaborative regulatory investigations and the development of new safety strategies to mitigate risks associated with Nitrosamine Drug Substance-Related Impurities (Aishwarya et al., 2025; Shabangu et al., 2022) The introduction of trace nitrite can be caused by raw materials, processing aids and excipients of natural or semi-synthetic origin and can result in nitrosation reactions in the manufacturing or storage process (Akkaraju et al., 2023; Moser et al., 2023).

Varenicline is a partial agonist of α42 nicotinic acetylcholine receptors that are selective and has been extensively utilized in smoking cessation treatment (Corrêa & Chatkin, 2023). The molecule has a secondary amine group which can be nitrosated in the presence of nitrosating agents under conducive microenvironmental factors to give rise to N-nitroso-varenicline (Vidyamani et al., 2024). Since the acidic environment and the presence of moisture encourage the process of nitrosation, the choice of formulation and excipients can have a strong impact on the risk of nitrosamine in the final dosage form (Berardi et al., 2023; Shakleya et al., 2024).

Secondary amines are typically nitrosated by the formation of nitrosating agents (e.g. NO+) through the action of nitrite under acidic conditions, and then electrophilically attacked on the nitrogen atom of the amine. The efficiency of reactions is determined by the state of protonation, electron density at the nitrogen atom, accessibility of the solvent, and mobility of the molecule. Thus, the probability of nitrosamine formation can be inhibited with mitigation methods that lower the availability of amines, lower the nucleophilicity, decrease the diffusion of nitrite, or regulate the pH of the microenvironment.

Intimate mixing of drugs with polymeric carriers is a common method to modify the solid-state properties of drugs, such as crystallinity and molecular mobility, with solid dispersion systems (Siepmann et al., 2021). In addition to the ability to improve the solubility, polymer matrices can tune chemical reactivity by facilitating non-covalent interactions and limiting local mobility (Ghanem et al., 2013; Fridgeirsdottir et al., 2018; Schammé, 2016; Wilke et al., 2024). Understanding these polymer–drug interactions is critical for predicting the physical stability and chemical behavior of the API within the matrix (Saerens et al., 2012). A derivative of hydroxyl-rich polysaccharide, maltodextrin, provides a high density of hydrogen-bonding interactions that can react with polar functionalities in embedded molecules of drugs.

We present a proposal of hydrogen-bond mediated microenvironmental shielding of varenicline in a maltodextrin-based solid dispersion as a proactive formulation-level intervention to reduce the risk of nitrosation and we compare this polymer-based system with a small-molecule interaction model in cysteine. The evaporation of the solvent was done with the help of a rotavapor to enhance the dispersion of varenicline at the molecular level in maltodextrin and the reduction of the time spent in the presence of water, and then the direct-compression tablet development was conducted with the use of low-nitrite excipients and sodium citrate to control the pH (pH > 6). Molecular docking was modified into a physicochemical association model to describe viable hydrogen-bond interactions between varenicline and maltodextrin and cysteine was used as a comparator to place the interaction mechanism into context.

The aim of this work was to offer mechanistic, molecular-level assistance to excipient engineering and solid-dispersion design as preventive strategies to reduce the chance of nitrosation in amine-containing pharmaceuticals with varenicline as a case study.

2. MATERIALS & METHODS

2.1 Materials

The active pharmaceutical ingredient (API) was varenicline tartrate (equivalent to 1 mg varenicline per tablet). Maltodextrin was used as the polymeric carrier to prepare solid dispersion. The excipients used to prepare the tablets were microcrystalline cellulose, croscarmellose sodium, stearic acid and sodium citrate. The choice of all excipients was aimed at reducing the content of nitrite to a minimum to reduce the possible presence of nitrosating species. Processing solvents were methanol and purified water, which were used in the preparation of solid dispersion by rotavapor.

2.2 Preparation of Varenicline–Maltodextrin Solid Dispersion by Rotary Evaporation

To facilitate close mixing of the molecules and microenvironmental protection of the nitrosatable amine, solid dispersion was prepared by a solvent evaporation technique with the help of a rotavapor to ensure the solvent was completely evaporated. Varenicline tartrate and maltodextrin were mixed in a mixture of methanol and water and the mixture stirred to form a homogenous mixture. Rotary evaporation under reduced pressure and controlled temperature was applied to the solution to slowly extract the solvents out of the solution and leave behind a dried polymer-impregnated drug dispersion. This was done to decrease the crystallinity of the active pharmaceutical ingredient (API) and enhance its amorphous nature. Moreover, it improves hydrogen-bonding between

varenicline and maltodextrin, which promotes the dispersion of the molecular level of the polymer matrix. The inclusion of the amine functionality into the hydroxyl-rich maltodextrin structure further restricts solvent accessibility, and the controlled evaporation conditions reduce the length of time the formulation is exposed to aqueous conditions, further enhancing the stability of the formulation.

2.3 Tablet formulation by direct compression

Dried varenicline-maltodextrin solid dispersion was mixed with other excipients and compressed using direct compression to obtain tablets with a target weight of 200 mg. Sodium citrate was added to ensure that the microenvironmental pH was kept over 6 and thus, generation of nitrosating species in acidic conditions was minimized.

Table 1. Composition used for preparation of varenicline-maltodextrin solid dispersion and final tablet blend (per tablet equivalent).

Steps	Process stage	Ingredient	Amount (mg/tablet)
1	Solid dispersion (rotavapor)	Varenicline tartrate (equivalent to 1 mg varenicline)	1.53
		Maltodextrin	15.30
		Methanol (processing solvent)	50.00
		Purified water (processing solvent)	50.00
2	Direct compression	Varenicline-maltodextrin solid dispersion (from Step 1, after solvent removal)	16.83
		Maltodextrin	86.17
		Microcrystalline cellulose	65.00
		Sodium citrate	20.00
		Croscarmellose sodium	10.00
		Stearic acid	2.00
		Total tablet weight	200.00

Note: Solid-dispersion preparation was done only in the presence of Methanol and purified water and these were removed by rotary evaporation; quantities indicated of solvents are per-tablet equivalents used in processing.

2.4 Molecular modelling and docking studies

Three-dimensional structures of varenicline, maltodextrin (representative oligomeric fragment), and cysteine were prepared and refined using UCSF Chimera v1.16 (Pettersen et al., 2004). Energy minimization was carried out using the AMBER force field, and AM1-BCC charges were assigned to support electrostatic representation during docking simulations. Prepared structures were converted to PDBQT format using AutoDockTools (ADT) v1.5.6 (Morris et al., 2009) for compatibility with AutoDock Vina v1.2.7 (Eberhardt et al., 2021; Trott and Olson, 2010).

Docking was performed to model physicochemical drug–polymer association rather than biological receptor binding. These computational approaches, including quantum chemical calculations, help to clarify activation and deactivation pathways essential for carcinogenicity risk assessment (Goller et al., 2024). Varenicline was treated as a flexible ligand (rotatable bonds defined), maltodextrin was treated as rigid to approximate a constrained solid-state microenvironment, and cysteine was treated as a flexible comparator molecule.

Docking in AutoDock Vina v1.2.7 was conducted using a 25 Å × 25 Å × 25 Å grid box, centered at X = −1.01, Y = 0.26, Z = −0.54 for the maltodextrin fragment, with an exhaustiveness of 16, nine output modes (num_modes = 9), and an energy range of 3 kcal/mol.

Docked complexes were ranked by docking affinity score. Conformational similarity was evaluated by RMSD-based clustering, and the lowest-scoring pose within the most populated cluster was selected for interaction analysis. Hydrogen-bond geometries were visualized and measured using BIOVIA Discovery Studio Visualizer (BIOVIA, 2021).

Three-dimensional structures of varenicline, maltodextrin (representative oligomeric fragment) and cysteine were made and refined with UCSF Chimera v1.16 (Pettersen et al., 2004). The AMBER force field was used to optimize the energy and AM1-BCC charges were applied to facilitate the electrostatic representation when docking simulations were performed. AutoDockTools (ADT) v1.5.6 was used to convert prepared structures to PDBQT format to be compatible with AutoDock Vina v1.2.7 (Morris et al., 2009; Eberhardt et al., 2021; Trott and Olson, 2010).

Docking was also used to simulate physicochemical drug-polymer interaction as opposed to biological receptor interactions. Varenicline was considered as a flexible ligand

(rotatable bonds were defined), maltodextrin was considered as rigid to simulate a constrained solid-state microenvironment and cysteine was considered as flexible comparator molecule.

AutoDock Vina v1.2.7 docking was performed with a grid box of 25 Å x 25 Å x 25 Å (including the maltodextrin fragment at X = −1.01, Y = 0.26, Z = −0.54) with an exhaustiveness of 16, nine output modes (num modes = 9) and an energy range of 3 kcal/mol.

Docked complexes were ranked based on docking affinity score. RMSD-based clustering was used to assess conformational similarity and the pose with the lowest score in the most populated cluster was chosen to be analyzed in terms of interaction. BIOVIA Discovery Studio Visualizer was used to visualize and measure hydrogen-bond geometries (BIOVIA, 2021).

3. RESULTS AND DISCUSSION:

3.1 Docking study of the interaction between varenicline-maltodextrin

Molecular docking indicated that varenicline is capable of interacting well with maltodextrin, which is a favorable indicator of the possibility of hydrogen-bond mediated microenvironmental shielding in a polymer matrix. The highest docking pose scored a docking affinity of -2.66 kcal/mol, which is in agreement with possible non-covalent interaction with the Vina scoring functionality. Interaction mapping revealed that varenicline and maltodextrin were interacting through a conventional hydrogen bond with an interatomic distance of 2.84 A, which is in line with a stabilizing hydrogen-bonding interaction.

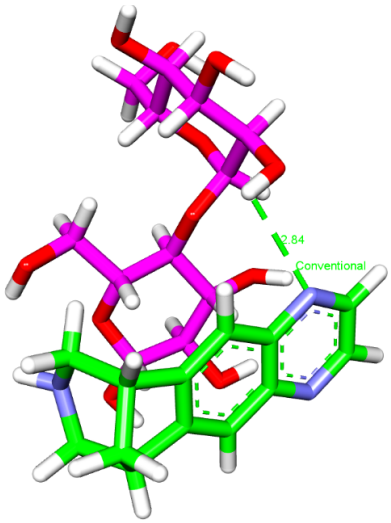


Figure 1. Pose of varenicline represented by a fragment of a maltodextrin molecule with a stabilizing hydrogen bond (2.84 Å)

In spite of the fact that the absolute docking score demonstrates moderately strong interaction, it is often the case that drug-polymer systems in solid dispersions are dictated by a number of weak, cooperative non-covalent interactions. Multivalent hydrogen-bonding capacity is presented by the hydroxyl rich environment of maltodextrin, and can be used concertedly to reduce local mobility and solvent accessibility around the nitrosatable amine.

3.2 Docking study of the interaction between varenicline-cysteine

Docking of varenicline with cysteine, a small-molecule comparator, was also done to verify the hydrogen-bonding propensity of varenicline. The binding affinity of the varenicline-cysteine complex was -2.65 kcal/mol which was equivalent to the maltodextrin system. Formation of hydrogen-bonds was seen (two hydrogen-bonds were found in the docking output, labeled H1 and H6), and the best pose had a representative distance of about 2.55 Å.

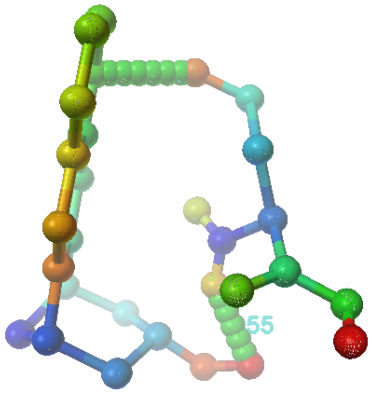


Figure 2. Varenicline and cysteine representative docked pose (hydrogen-bond formation) (representative distance = 2.55 Å)

The structural and formulation implications are different even though the docking scores were similar. Cysteine is able to offer localized, small-molecule hydrogen bonding, but is not able to offer steric encapsulation and multivalent interaction network that can be found in a polymeric matrix. Also, cysteine includes reactive functional groups (e.g., thiol), which can increase stability issues in solid dosage forms.

3.3 Mechanistic implications of susceptibility to nitrosation

The nitrosation of secondary amines is preferable in the presence of acids, in which nitrite has the capability to form nitrosating species. To this end the proposed formulation is a combination of various complementary controls that are aimed at suppressing the risk of nitrosation. First, H bonding of maltodextrin hydroxyl groups with the amine-binding area of varenicline can potentially decrease the accessibility of amines locally and the exposure of nitrosating agents. Second, the entrapment of the API in solid-dispersion matrix decreases the mobility of molecules and may limit the diffusion of nitrite to the drug microenvironment. Third, sodium citrate is added to ensure a microenvironmental pH above 6, which prefers the avoidance of nitrosating intermediates formation under locally acidic conditions. Lastly, excipients are chosen based on low nitrite levels to narrow down the general pool of available nitrosating species.

3.4 Comparative analysis and justification of choice of maltodextrin

Both cysteine and maltodextrin were found to have an effective hydrogen bonding with varenicline in docking simulations (binding affinities of about -2.65 to -2.66 kcal/mol). However, excipient selection for a mitigation strategy must consider more than docking score, including solid-state stability, manufacturability, and regulatory acceptability. Table 2 summarizes key formulation-relevant differences between cysteine and maltodextrin.

Table 2. The most important formulation-relevant differences between cysteine and maltodextrin.

Parameter	Cysteine	Maltodextrin
Hydrogen bonding ability	Yes	Yes (multivalent)
Polymer matrix formation	No	Yes
Solid dispersion compatibility	Limited	Excellent
Stability in solid dosage form	Risk of oxidation	High stability
Organoleptic impact	Possible odor issues	Neutral
Regulatory acceptance as excipient	Limited use	Widely accepted
Risk of introducing new reactive species	High (thiol oxidation)	Low
Scalability	Moderate	High

Overall, the choice of maltodextrin as the carrier of choice is based on the ability to offer sustained microenvironmental protection via polymeric encapsulation, solid dispersion production and good stability and regulatory properties. The aim of this excipient-engineering strategy is to be a formulation-level, proactive approach to reducing the risk of nitrosamine in amino-containing APIs.

3.5 Limitations and future work

The docking analysis in this paper was employed as an interaction-feasibility model and does not quantitatively

measure solid-state binding free energy or experimentally validate the nitrosamine suppression. Since maltodextrin was modeled as an oligomeric fragment, which was modeled as rigid, the simulated interaction geometry can be different than the dynamic, heterogeneous microenvironment of an amorphous solid dispersion. Future efforts ought to experimentally confirm hydrogen-bond formation and amorphization (e.g. FTIR, DSC, and PXRD), measure the levels of nitrite in excipients and determine the formation of N-nitroso-varenicline under accelerated/stress storage using a validated LC-MS/MS assay.

4. CONCLUSION

This paper suggests an excipient-engineering strategy consisting of the maltodextrin-based solid dispersion design (matrix shielding and low molecular mobility), microenvironmental pH regulation with the help of sodium citrate (target pH > 6), and excipient nitrite reduction to reduce the chances of N-nitroso-varenicline formation in varenicline solid dosage forms.

Docking was employed as an interaction-feasibility model and it supported hydrogen-bond formation between varenicline and maltodextrin (docking affinity -2.66 kcal/mol; hydrogen-bond distance 2.84 Å) and between varenicline and cysteine (docking affinity -2.65 kcal/mol; representative hydrogen-bond distance -2.55 Å). Although the docking scores were similar, maltodextrin is the only multivalent polymer matrix that can be encapsulated sustainably, and cysteine is a localized small-molecule interaction partner and can bring about extra solid-state stability concerns (e.g., thiol oxidation).

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