International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Varenicline and Maltodextrin Combination: A Promising Approach for Reducing Nitrosamine Impurities in Solid Dosage Forms

SRK Raju Sagiraju[1], Erdi EKMEKCİ[2], Emre Erol ALDENİZ[3], Udaya DUDE[4], Ceren GOKALP AYMAN[5]

[1]Project Leader, Abdi İbrahim Pharmaceuticals
[2]Supervisor, Abdi İbrahim Pharmaceuticals
[3]Manager, Abdi İbrahim Pharmaceuticals
[4]Director, Abdi İbrahim Pharmaceuticals
[5]Specialist, Abdi İbrahim Pharmaceuticals

Abstract
This research article investigates the use of varenicline and maltodextrin combination to reduce the nitrosamine impurities in varenicline tablets, a medication used to treat nicotine addiction. Nitrosamines are carcinogenic compounds that have been found in varenicline, raising concerns about its safety. Drug excipient compatibility was initially performed with all possible excipients, including maltodextrin, to identify potential approaches for reducing nitrosamine impurities. The results showed that maltodextrin was more effective than other excipients in reducing nitrosamines in the drug product. This finding provided an indication for the use of maltodextrin as a potential solution to the nitrosamine problem in varenicline tablets. The study involved preparing varenicline-maltodextrin formulations and analyzing the formulations for nitrosamine impurities. The finished formulation was prepared by simple mixing of varenicline, maltodextrin, disintegrant, filler, lubricant, and compression using suitable tooling, followed by aqueous film coating. The formulated tablets were tested for assay, content uniformity, dissolution in release media, and multimedia, and the results were found to be satisfactory. The results showed that the varenicline-maltodextrin combination significantly reduced nitrosamine content, and all other parameters were satisfactory. In addition, the nitrosamine impurity levels were significantly reduced to less than 3 ppm after 30 days of storage at 50±2°C/75±5 % RH. Moreover, more than 85% of drug release was observed in all tested release media, meeting the predefined specifications for BCS-based biowaiver. These findings suggest that the use of varenicline and maltodextrin combination is a promising approach to improve the safety of varenicline.

Keywords: Nitrosamines, Varenicline Tartrate, Maltodextrin and Varenicline combination

1. Introduction:

Varenicline is a prescription medication that aids in the cessation of smoking. In recent years, varenicline products have come under investigation due to the presence of nitrosamine impurities, which are proven carcinogens. Nitrosamines are a class of chemical compounds that are formed during certain manufacturing processes and can be present in trace amounts in pharmaceutical products. The presence of

nitrosamines in varenicline products has led to several product recalls and warnings by regulatory agencies. In 2019, the US Food and Drug Administration (FDA)[i] issued a safety alert regarding the presence of nitrosamines in some varenicline products

Table *1*. The FDA found that some varenicline products contained nitrosamine impurities above the acceptable daily intake limit, posing a potential risk to patients. The FDA recommended that patients continue taking their medication as directed and contact their healthcare provider if they had any concerns. Nitrosamines are known carcinogens associated with an increased risk of cancer. These impurities in pharmaceutical products have raised concerns among patients and regulatory agencies. The European Medicines Agency (EMA) [ii] has also issued guidance on the detection and control of nitrosamine impurities in pharmaceutical products.

The EU[iii], and Canada[iv] have a limit of 400 ng/day for N-nitroso-varenicline impurity. To address the problem of nitrosamine impurities in varenicline products, there is a need for the development of nitrosamine-free formulations. In this context, Abdi İbrahim İlaç Sanayi A.Ş, Turkey, conducted research on the varenicline and maltodextrin combination as a potential approach to reducing nitrosamine impurities in solid dosage forms. Maltodextrin is a carbohydrate that is commonly used as a diluent or filler in pharmaceutical formulations.

The aim of this study is to evaluate the potential of varenicline and maltodextrin combinations for reducing nitrosamine impurities in varenicline solid oral dosage forms. The study also investigates the efficacy of the formulation in terms of the assay, content uniformity, dissolution in release media, and multimedia. The findings of this study may provide valuable insights into the development of safer and higher quality varenicline products for patients.

2. Background:

Varenicline is a medication used to treat nicotine addiction. It is a partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes and binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors.

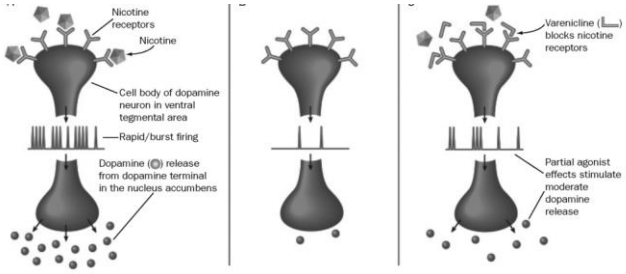

Figure 1 :Mechanism of action of Varenicline

The efficacy of varenicline in smoking cessation is believed to be the result of varenicline's activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to $\alpha_4\beta_2$ receptors.

Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine.

C_{max} attains typically within 3-4 hrs. after oral administration, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%[v]

Varenicline was first approved by the US Food and Drug Administration (FDA) in 2006, under the brand name of Chantix and it has since become a popular treatment for smoking cessation.

Nevertheless, nitrosamines, which are carcinogenic chemicals that can cause cancer in humans, have been identified in varenicline. Nitrosamines are generated when nitrites, which are extensively employed as food and pharmaceutical preservatives, react with amines found in varenicline.

3. Research:

A study was conducted to investigate the use of varenicline and maltodextrin combination to reduce the nitrosamines in the drug product. The study involved preparing varenicline-maltodextrin formulations with different ratios of varenicline to maltodextrin. The formulations were then analyzed for nitrosamine content.

Drug excipient compatibility was originally undertaken with all available excipients, including maltodextrin, to explore viable ways to lower nitrosamine impurities. Maltodextrin was shown to be more successful than other excipients in decreasing nitrosamines in the drug product. This finding suggested that maltodextrin may be used as a potential solution to the nitrosamine issue in varenicline tablets **Table 2**. The manufacturing process involves simple mixing of varenicline, maltodextrin, disintegrant, filler, Lubricant, and compression using suitable tooling, followed by aqueous film coating.

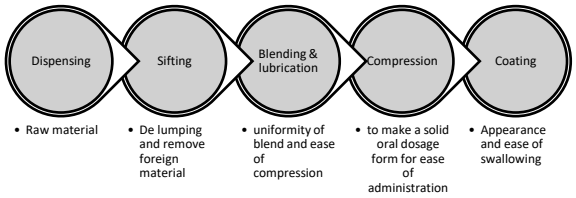

Figure 2: Manufacturing process of varenicline tablets

The ingredients are first mixed together in the desired proportions to ensure uniformity of the final product. The mixed ingredients are then compressed using suitable tooling, such as a rotary tablet press, to form tablets of the desired weight, size, and shape. Finally, the tablets are coated with an aqueous film coating to improve their appearance, acceptability, and stability, protect them from environmental factors such as moisture, and aid in swallowing

Table 3.The use of suitable excipients and compression parameters can ensure the quality and efficacy of the final product, while aqueous film coating can improve its acceptability and stability

The combination of varenicline and maltodextrin was found to be effective in reducing nitrosamines to less than 3 ppm, which is within the acceptable limit set by regulatory agencies. The study also tested the stability of the formulation at 50±2 °C / 75±5 % RH for 30 days in packed condition, indicating that the formulation is stable under these conditions **Table 4**.

The study found that the varenicline-maltodextrin combination significantly reduced the nitrosamine content in the drug product. The study also found that the varenicline-maltodextrin combination did not affect the physical **Table 5** or chemical **Table 6** properties of varenicline, assay, content uniformity, dissolution in release media, and multimedia testing are essential parameters to evaluate the quality and

efficacy of the drug product. It is reassuring to know that all these parameters have been tested for the varenicline and maltodextrin batches, and the results are satisfactory.

The dissolution profile of a drug product in different release media is an essential parameter to evaluate the product's quality and efficacy. The results have indicated that the varenicline and maltodextrin formulation releases more than 85% of the drug in all tested media, **Table 7** which meets the predefined specifications for BCS-based biowaiver.

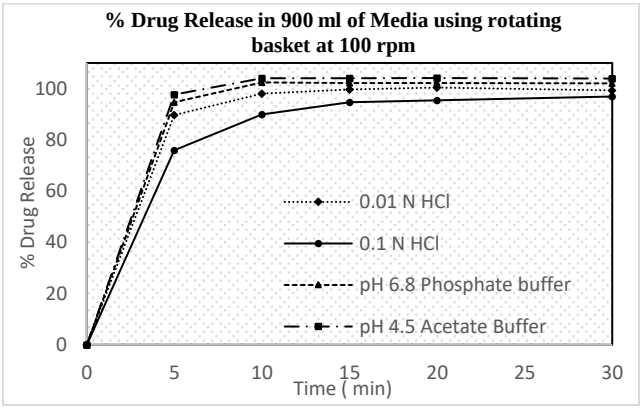

Figure 3: Multimedia dissolution of varenicline tablets 1 mg film coated tablets.

The tested media, 0.1 N HCl, 0.01 N HCl, pH 4.5 Acetate buffer, and pH 6.8 Phosphate buffer, represent the physiological pH ranges in the stomach and small intestine. The high dissolution rate of the varenicline and maltodextrin formulation in all these media indicates that the drug product is likely to be well-absorbed in the body and therefore effective in treating nicotine dependence.

The dissolution test evaluates the ability of the drug product to release the API in the desired amount and at the desired rate in the release media. The multimedia testing evaluates the effect of various media (such as gastric and intestinal fluids) on the release of the API from the drug product. Overall, the satisfactory dissolution profile of the varenicline and maltodextrin formulation in different release media is a positive indication of its quality and efficacy.

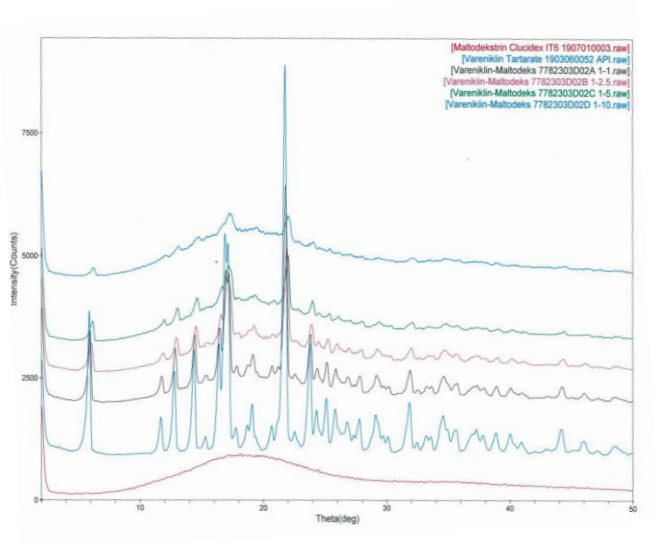

Figure 4: XRD Diffractogram of Varenicline tartrate, maltodextrin, Varenicline tartrate and Maltodextrin combinations (1:1, 1:2.5, 1:5, 1:10)

The X-ray diffraction (XRD) analysis of Varenicline tartrate and Maltodextrin mixtures, prepared in ratios ranging from 1:1 to 1:10, revealed consistent diffraction patterns corresponding to Varenicline tartrate's characteristic 2 theta values across all ratios. No significant shifts or alterations in peak positions were observed, indicating the preservation of Varenicline tartrate's crystalline structure. These findings suggest minimal to no interaction between Varenicline tartrate and Maltodextrin, signifying a state of physical admixture rather than molecular interaction. This underscores the compatibility of the components in solid-state formulations and provides insights for the development of optimized Varenicline tartrate formulations.

4. Conclusion:

In conclusion, the use of varenicline and maltodextrin combination can significantly reduce the nitrosamine content in varenicline. This combination does not affect the physical or chemical properties of varenicline.

The reduction of nitrosamine impurity levels in the varenicline and maltodextrin formulation is a significant finding, as nitrosamines are a known class of carcinogenic impurities that have been found in several pharmaceutical products.

The use of maltodextrin as an excipient in the formulation is a likely contributor to this reduction in nitrosamine impurity levels. It is worth noting that the reduction in nitrosamine impurity levels in the varenicline and maltodextrin formulation may not only improve the safety of the product for patients but also reduce the risk of recalls and regulatory actions by health authorities. The presence of nitrosamine impurities has led to several product recalls and warnings by regulatory agencies in recent years, highlighting the importance of minimizing their presence in pharmaceutical products.

Overall, the significant reduction of nitrosamine impurity levels in the varenicline and maltodextrin formulation compared to other marketed products is a promising finding that may improve the safety and quality of this drug product for patients.

Table 1: Laboratory analysis of varenicline marketed products by USFDA

Company (Manufacturer)	Product	Lots Tested	N-nitroso-varenicline level in micrograms/tablet (nanograms/tablet)	N-nitroso-varenicline level in parts per million (ppm)
Pfizer	Chantix (varenicline) 1mg	EA6080, EC9841, EC9847, EC9848, EX2099, DR5086	0.15-0.47 (150-470)	155-474
Par Pharmaceuticals	Varenicline 1 mg	31960807, 31960801	0.003 (3)	3
Apotex	APO-Varenicline Tartrate 1 mg)	TG2183, TG2181, TG2182	0.027-0.044 (27-44)	27-44
Apotex	APO-Varenicline Tartrate 0.5 mg	TG2180, TG2178, TG2179	0.014-0.021 (14-21)	27-42

Table 2: Drug excipient compatibility studies

No.	Drug excipient combination	IMP VC-09	IMP NDEA	IMP VC-09	IMP NDEA
		Limit = 18.5 ppm	Limit = 13.25 ppm	Limit = 18.5 ppm	Limit = 13.25 ppm
		Initial		**50^0/75% RH – 15 days**	
1	Varenicline Tartrate: Microcrystalline cellulose	5.40	BDL	11.20	BDL
2	Varenicline Tartrate: Maltodextrin granule (Direct blending)	2.81	BDL	1.97	BDL

Table 3: Composition of Varenicline tablets prototype

Function	% w/w
Varenicline	0.855 mg or 1. 71 mg
Maltodextrin	1 to 20 %
Disintegrant	0.5 to 5%
Filler	75% to 85%
Lubricant	0.5 to 5%
Coating Agent	3 to 7%

Disintegrant: Sodium starch glycolate, Crospovidone, and Croscarmellose sodium
Filler: Dibasic calcium phosphate, Silicified microcrystalline cellulose, Lactose monohydrate, and Starch
Lubricant: Magnesium stearate, Sodium stearyl fumarate, zinc stearate, and calcium stearate

Table 4: Nitrosamines data at initial and 50^0/75% RH stress condition at 15 and 30 days

Storage condition	Initial		50^0/75% RH		50^0/75% RH	
			15 days		30 days	
Nitrosamine Impurities	**VC-09**	**NDEA**	**VC-09**	**NDEA**	**VC-09**	**NDEA**
Plain Alu Alu Blister	TE	TE	2.01	TE	1.75	TE
Desiccant Alu Alu Blister	TE	TE	1.14	TE	1.72	TE

Table 5: Physical Properties of Core and Coated Tablets

Parameter	Uncoated Tablets	Coated Tablets
Weight	200 mg (191 mg to 203 mg)	210 mg (208 mg to 213 mg)
Thickness	3.60 mm (3.50 mm-3.50 mm)	3.70 mm (3.60 mm -3.80 mm)
Hardness	14.5 kp (10.5 kp-18.20 kp)	18.5 kp (16.60 kp-19.50 kp)
Disintegration time	05 min 50 sec	08 min 45 sec
Friability	0.05 %	NA

Table 6: Chemical Characterization of finished formulation varenicline tartrate 1 mg film coated tablets

Tests	**Results**
Dissolution in 0.01N HCl at 15 min	101.0 (RSD: 1.8) (Basket @ 100 rpm)
Assay	97.9 %
Content Uniformity	99.9 % (98.2 %-102.7 %) SD: 2 & AV: 4.8
Impurity Name	**Result**
RRT~ 0.889	<LOQ
RRT~ 1.332	0.01
RRT~ 1.388	<LOQ
RRT~ 1.426	0.02
Total IMP	0.03

Table 7: Multimedia Dissolution of finished formulation varenicline tartrate 1 mg film coated tablets

Varenicline tartrate 1 mg film coated tablets					
100 rpm, Basket, 0.01N HCl			**100 rpm, Basket, 0.1N HCl**		
Time (min)	**% Drug Released**	**RSD**	**Time (min)**	**% Drug Released**	**RSD**
5	89.6	10.4	5	75.9	19.5
10	98.0	4.0	10	89.9	12.6
15	99.6	1.6	15	94.6	7.8
20	100.4	2.2	20	95.4	5.9
30	99.3	0.6	30	96.9	2.3
100 rpm, Basket, pH 6.8 Phosphate Buffer			**100 rpm, Basket, pH 4.5 Acetate buffer**		
Time (min)	**% Drug Released**	**RSD**	**Time (min)**	**% Drug Released**	**RSD**
5	94.7	3.6	5	97.6	3.3
10	102.4	2.1	10	104.0	0.3
15	102.1	2.0	15	104.0	0.5
20	102.2	2.1	20	104.1	0.1
30	102.0	2.0	30	103.9	0.2

References:

1. US FDA updates and press announcements nitrosamine varenicline Chantix
2. EMA Post Authorization Referral Procedures on Nitrosamine Impurities
3. EMA Q&A Appendix 1 update posted Sept 28, 2023
4. Guidance on nitrosamine impurities in medications updated on October 20 2023
5. Chantix patient Information label