

Date report created  
2020-01-08

Project name  
ZYN PMTA

Project nr  
N.A.

Report nr  
N.A.

Created by  
(b) (6)

Created by title  
Research Scientist

Created by department  
APRS

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# Function of the Nicotine Salt in ZYN

## Comparison with Nicotine Salts in Electronic Nicotine Delivery Systems

### Summary

ZYN pouches contain nicotine in the form of the bitartrate dihydrate salt. In the salt form, nicotine is much less sensitive to oxidation and evaporation. This results in a much longer shelf life than if nicotine would have been present in the freebase form. Because mucosal absorption occurs very slowly for nicotine in the salt form, the nicotine must be converted into the freebase form before nicotine uptake can occur.

(b) (4). Thereby, the ZYN product utilizes the increased stability of nicotine in its salt form during storage, while still providing satisfactory delivery of freebase nicotine to the consumer upon use.

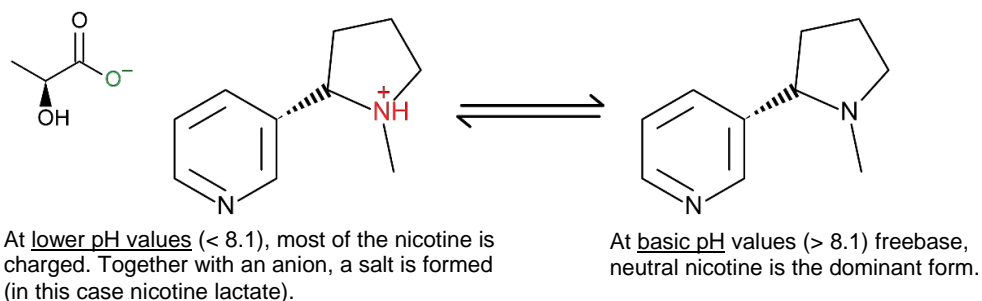
Some electronic nicotine delivery systems (ENDS) also contain nicotine salts. (b) (4)

(b) (4). In ENDS, nicotine salts facilitate the inhalation of greater concentrations of nicotine by reducing the irritation of the throat that is associated with freebase nicotine, as well as allowing a larger fraction of the nicotine to reach the lungs because less is deposited in the mouth and throat. Consequently, the use nicotine salts in ENDS result in a faster and larger uptake of nicotine, and an uptake profile that resembles that from traditional combustible cigarettes. (b) (4)

### Background

In the salt form, as in the ZYN pouches, (b) (4). The form of nicotine changes in response to the pH, as shown in Figure 1. At low to neutral pH values, most of the nicotine is positively charged, and combines with negatively charged ions to form salts. As with other highly polar molecules, positively charged nicotine (as in a salt) is essentially unable to pass through biological membranes and reach the blood. Thus, for uptake to occur the nicotine salt must react with a base or buffering agent that maintains a higher pH value, thereby forming freebase nicotine which can easily pass through biological membranes into the blood. (b) (4)

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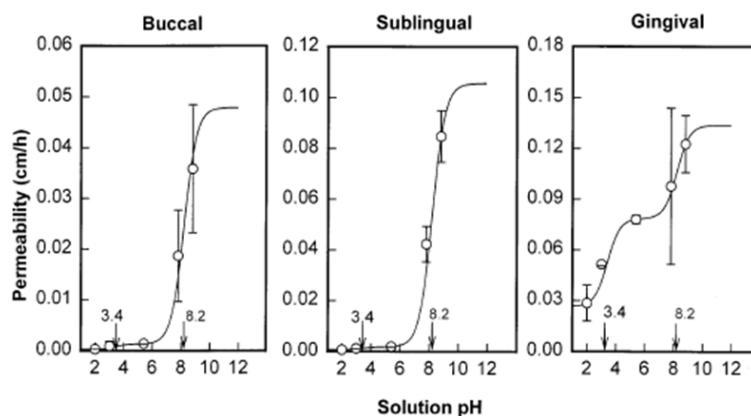
**Figure 1.** Illustration of equilibrium between charged nicotine (at neutral to low pH values) and freebase nicotine (at higher pH values). The charged form present at lower pH values forms salts together with anions (as an example, nicotine lactate is shown).

## Function of the Nicotine Salt in ZYN Pouches

The reason for using nicotine salts in ZYN pouches (b) (4)

Nicotine salts are protected from evaporation and oxidation, and thereby the product maintains its nicotine content throughout its shelf life. (b) (4)

At low pH values, in which the salt form nicotine is the major species, passage through the oral mucosa is very slow, as shown in [Figure 2](#). For uptake to occur through the mucosa, the nicotine salt (in which nicotine is positively charged) must be converted into the neutral (freebase) form ([Chen et al 1999](#)).



**Figure 2.** The relationship between the permeability of nicotine at different pH values for different types of oral mucosa. For all three types, it is clear that the freebase form of nicotine, which predominates at pH >8.2, passes through much more rapidly than the salt forms that dominate at lower pH values.

Source: [Chen et al 1999](#).

(b) (4)

## (b) (4)

### Function of Nicotine Salts in ENDS

Electronic nicotine delivery systems aerosolize a solution of nicotine which is then inhaled. The part of the nicotine that reaches the lungs is rapidly taken up into the blood. The use of nicotine salts (as opposed to freebase nicotine) in ENDS results in a faster and larger uptake of nicotine due to two reasons:

1. Nicotine salts cause much less irritation to the throat upon inhalation than freebase nicotine – thereby it is possible to use greater nicotine concentrations in the vapor without causing excessive irritation ([Caldwell et al 2012](#)).
2. The use of nicotine salts in ENDS results in a more efficient transfer to the lungs, because less of the nicotine is deposited in the mouth and throat than would be the case if freebase nicotine were used. In the lungs, the nicotine is rapidly buffered by the lung's extravascular fluid and thereby a fraction is converted into the bioavailable, freebase form. Because transfer from the lungs to systemic circulation is much faster than it is from the mouth or throat, the blood levels of nicotine rise much more rapidly when nicotine salts are inhaled, as compared to freebase nicotine ([Caldwell et al 2012](#); [O'Connell et al 2019](#)).

For these two reasons, ENDS using nicotine salts provide a rapid and large rise in plasma nicotine, thereby closely emulating the nicotine delivery profile obtained from smoking traditional combustible cigarettes.

### References

#### **Caldwell et al 2012**

Caldwell B, Sumner W, and Crane J. A Systematic Review of Nicotine by Inhalation: Is There a Role for the Inhaled Route? *Nicotine Tob Res*, 2019;14:1127–1139.

#### **Chen et al 1999**

Chen LLH, Chetty DJ, Chien YW. A mechanistic analysis to characterize oramucosal permeation properties. *Int J Pharm* 1999; 184:63–72.

#### **O'Connell et al 2019**

O'Connell G, Pritchard JD, Prue C, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med* 2019; 14:853–861.

#### **US 9,161,908**

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