REVIEW ARTICLE

Review of the evidence that pH is a determinant of nicotine dosage from oral use of smokeless tobacco

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Abstract

Objective—To determine whether manipulation of the pH of moist-snuff products by manufacturers could control the delivery of nicotine.

Data sources—Medline database 1966–97 using the following subject headings and keywords: nicotine, absorption, mouth mucosa, skin, hydrogen-ion concentration, smokeless tobacco, biological transport, and membranes; computer database of the tobacco bibliography maintained by the US Centers for Disease Control and Prevention's Office on Smoking and Health; bibliographies of pertinent journal articles, books, and governmental reports; personal communications with experts in nicotine pharmacology and addiction; and Brown & Williamson Tobacco Corporation documents in the Tobacco Control Archives of the University of California, San Francisco.

Study selection—Included all relevant animal studies, in-vitro studies, nicotine replacement therapy trials, and human observational studies.

Data synthesis—We found that the effects of pH on drug absorption have been well established in animal models for nicotine and many other acidic or basic compounds. Increased alkalinity promotes the absorption of nicotine and increases its physiological effects. Human studies, which are more limited, confirm these processes. For example, nicotine absorption is directly related to the pH when nicotine is delivered in either tobacco smoke or nicotine polacrilex gum.

Conclusions—Although other factors could influence the rate of nicotine absorption from oral tobacco, manipulating tobacco pH appears to be the primary means by which the speed of nicotine absorption is determined in moist-snuff products.

(*Tobacco Control* 1997;6:219–225)

Keywords: smokeless tobacco; nicotine; pH

Background

Nicotine is an addictive drug that is primarily responsible for tobacco dependence.¹ Administration of this alkaloid increases the expression

(“growth”) of nicotine receptors in the nervous system, which is associated with the development of tolerance and physical dependence. Nicotine also produces reinforcement by virtue of its effects in the brain, as well as a variety of effects on mood, cognition, and appetite that are also important pharmacological determinants of tobacco use.² Nicotine need not be delivered in tobacco to exert these effects, but that vehicle appears to maximise its addictive and toxic effects²; tobacco can rapidly deliver large amounts of this drug while permitting the user to substantially control the dosage.³ Both adolescents and adults who have used oral (smokeless) tobacco have developed symptoms of substance dependence and the nicotine withdrawal syndrome.^{4–8} Many of the adverse health effects of smokeless tobacco use—which include oral and pharyngeal cancer,⁹ oral lesions,^{9–10} cardiovascular diseases,^{11–12} and possibly dental caries^{9–13}—result from long-term use caused by nicotine dependence.

Smokeless tobacco use can produce nicotine levels in venous blood as high as those seen with cigarette smoking.¹¹ For both products, nicotine intake is directly related to difficulty in quitting and to symptoms of withdrawal.^{1–6,8} Speed of absorption is also a major determinant of addiction and other related effects; a few milligrams of nicotine delivered rapidly via inhalation of cigarette smoke, intravenous injection, or a smokeless tobacco product with a high pH produces much stronger physiological and psychoactive effects than slowly administering 20 mg of nicotine via a nicotine transdermal patch.² That the rate of delivery can affect a drug's addictive qualities has been shown not only with nicotine but also cocaine and sedatives.^{14–16}

The rate of transfer (absorption) of a chemical across a physiological membrane is related to the concentration of the chemical and the amount that is present in the free-base form. Increasing the pH of nicotine transforms this drug into an un-ionised or free-base form that moves easily through biological membranes and is more readily absorbed than ionised forms such as nicotine salt. Tobacco naturally occurs in an acidic form and therefore is slow to release free-base nicotine unless buffered to alkaline levels. Because saliva contains bicarbonate, which acts as a pH buffering agent, especially at high flow rates,¹⁷ the

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un-ionization of nicotine occurs even in a neutral pH oral environment, but the process may take many minutes to occur. Eventually, nearly all the nicotine in smokeless tobacco may be absorbed if left in the oral cavity for a sufficiently long time period. However, the primary effect of an alkaline pH is an increase in the rate of nicotine absorption and, therefore, an enhancement of the drug's psychoactive and addictive properties.

Nicotine has a pKa (dissociation constant) of 8.02¹⁸: in an aqueous solution with a pH of 8.02, half the nicotine would be in its un-ionised form and half in its ionised (not readily absorbable) form. The Henderson-Hasselbach equation can be used to estimate the proportion of total nicotine that is un-ionised at a specific pH level¹⁹

$$\text{pH} = \text{pKa} + \log \frac{[\text{B}]}{[\text{BH}^+]}$$

$$\% \text{ un-ionised nicotine} = \frac{\frac{[\text{B}]}{[\text{BH}^+]}}{\frac{[\text{B}]}{[\text{BH}^+]} + 1} \times 100$$

where pKa = 8.02; [B] = amount of un-ionised nicotine and [BH⁺] = amount of ionised nicotine.

The 1986 Comprehensive Smokeless Tobacco Health Education Act requires all manufacturers of smokeless tobacco products sold in the United States to report the quantity of nicotine their products contain to the Office on Smoking and Health of the US Centers for Disease Control and Prevention (CDC).²⁰ Testimony by experts in nicotine chemistry and pharmacology before the US House of Representatives' Subcommittee on Health and the Environment on 29 November 1994,²¹ several peer-reviewed journal articles,²²⁻²³ and an analysis by the US Food and Drug Administration²⁴ (FDA) indicate that the pH levels vary widely across moist-snuff brands and suggest that the level strongly affects the rate and quantity of nicotine dosage the user receives. Additional concern is raised by recent laboratory studies that suggest that the brands of moist snuff most likely to promote nicotine addiction are also those with the greatest potential carcinogenicity.²⁵⁻²⁶

When smokeless tobacco is used, nicotine is extracted from the tobacco and then crosses the oral mucosa to enter the blood stream and subsequently the brain, where it exerts pharmacological effects that lead to addiction. As indicated by the Henderson-Hasselbach equation, the degree to which the nicotine in tobacco is present in its un-ionised form (also described as "bioavailable", "free nicotine", or "free-base nicotine" state) is a function of the tobacco's pH; at a higher (more alkaline) pH, more of the nicotine is in this un-ionised form. Indeed, several authors have suggested that knowing the total nicotine content of a smokeless tobacco product without knowing its pH is of little value in estimating the rate or quantity

of nicotine absorbed.²²⁻²³⁻²⁷ The pH of moist snuff may increase during prolonged storage, depending on temperature, moisture, and other conditions.²⁸⁻²⁹ It appears, however, that manufacturers can control the effective dose of nicotine by further altering the pH of the product through the addition of sodium carbonate or other alkaline buffering agents. In fact, sodium carbonate, sodium bicarbonate, ammonium carbonate, and calcium carbonate all appear on the publicly available list of ingredients added to smokeless tobacco by the 10 major manufacturers of these products for the American market,³⁰ and these substances have reportedly been used by smokeless tobacco manufacturers to control the pH of their products.²⁴⁻²⁷⁻³¹ The reported purpose of manipulating nicotine dosage is to provide products with low nicotine dosage to new users to facilitate their development of addiction; then, as tolerance develops, to provide the higher dosage levels necessary to sustain their addictions and satisfy their needs for stronger products.³⁻²⁴⁻²⁷⁻³¹

Because of the testimony before the House Subcommittee on Health and the Environment and the scientific evidence supporting the role of pH in controlling nicotine delivery from smokeless tobacco, the Office on Smoking and Health (OSH) requested from the major manufacturers of smokeless tobacco for the United States market information on the total nicotine content and the pH of all brands they sold in the country. In a letter to OSH dated 9 May 1995, the United States Tobacco Company (UST), which manufactures 82% of the moist snuff sold in the United States,³² denied that pH has any effect on "so-called 'free nicotine'". UST based its claim on an unpublished document dated 9 February 1995 and submitted to OSH that was prepared by Professor Jeffrey R Idle of the University of Newcastle in the United Kingdom (copies of this document are available on request). Professor Idle reviewed the literature on pH and nicotine absorption and discussed other factors that may influence nicotine absorption from smokeless tobacco products. He contended that it was untrue that a certain percentage of the nicotine in a snuff product is either free or immediately available to be absorbed and stated that in all tobacco products most of the nicotine is trapped inside the leaf particles. Professor Idle concluded, "In summary, it is not the pH of smokeless tobacco, but a variety of other chemical, biological and behavioral factors that are responsible for the degree of absorption of nicotine from smokeless tobacco."

In this paper we critically review the published evidence on the relation between absorption of nicotine across the mucosal lining of the oral cavity and the pH of the tobacco product in aqueous solution.

Data sources

Data for this review came from a variety of sources. We searched the Medline database from 1966 to 1997 to identify relevant published scientific literature by using the

following subject headings and keywords: nicotine, absorption, mouth mucosa, skin, hydrogen-ion concentration, smokeless tobacco, biological transport, and membranes. Additional published materials such as book chapters and conference proceedings were identified by searching the computer database of the tobacco bibliography maintained by the Office on Smoking and Health. We identified other relevant studies by examining the bibliographies of pertinent journal articles, books, and governmental reports. Other data, both published and unpublished, were identified through personal communications with experts in the field of nicotine pharmacology and addiction. Tobacco industry information was located through keyword searches of the Brown & Williamson Tobacco Corporation documents in the Tobacco Control Archives of the University of California, San Francisco.

Animal studies and models of pH-modulated absorption

The concept that an alkaloid's bases are better than its salts at penetrating certain biological membranes is at least a century old; in 1940, Travell cited an 1897 report from Moore and Row that found that nicotine base was about five times as active as nicotine hydrochloride when given subcutaneously.³³ Before reliable measures of nicotine or its metabolites in biological fluids became available, most researchers used physiological reactions to nicotine, such as death or blood pressure elevation, as a marker for dosage. For example, in a series of experiments reported in 1940³³ on the influence of pH on the absorption from the stomach of a number of alkaloids (including nicotine), Travell used death of the experimental animal as her standard. Travell found that injecting 50 mg per kg of body weight into the stomach of a cat was not lethal when the solution had an acidic pH of 1.2, but when the solution was buffered to an alkaline pH of 8.6, a dose of 20 mg/kg was fatal. Travell concluded that the pH of the solution was a major determinant of the absorption of nicotine and other alkaloids across the gastric mucosa. In a later study,³⁴ Travell found that increasing the pH of an aqueous solution of nicotine to alkaline levels enhanced the absorption of nicotine across intact skin, in the urinary bladder, and in subcutaneous injections.

Armitage and Turner,³⁵ who studied the physiological effects in cats of tobacco smoke from cigarettes and cigars absorbed through the oral mucosa, noted that cigarette smoke, which had a pH of 5.35 in their study, had virtually no effect on blood pressure or ear twitching when the smoke intake was surgically limited to the oral cavity. However cigar smoke, which had a pH of 8.5, caused a marked rise in blood pressure and increased ear twitching under the same conditions. Armitage and Turner also studied solutions of nicotine buffered to pH levels of 6, 7, and 8; they found that the rise in blood pressure associated with a nicotine concentration of 1.2 mg/ml at pH 7 was closely matched by a solution with a concentration of just 0.2 mg/ml buffered to

pH 8.³⁵ They concluded that the pharmacological response clearly depended on the amount of free-base nicotine in the mouth. These investigators also found that peak concentrations of nicotine in the carotid artery at pH 8 were about 2.5 times what they were at pH 7 and 4 times those at pH 6. Furthermore, at pH 8 the rate at which the levels of nicotine in the blood increased in the first 2–5 minutes was about 3.5 times the rate at pH 7 and 8 times the rate at pH 6.

Schievelbein *et al* performed similar experiments on dogs and found that a pH of 10.2 in the presence of total particulate matter (TPM) in solution resulted in much more rapid nicotine absorption in the blood than a pH of 7.4.³⁶ They also found that the mean nicotine level at nearly all time intervals from 1 to 15 minutes following oral application of 5 mg nicotine per kg body weight was higher at pH 10.2 than at pH 7.4. They concluded, however, that there were no differences in nicotine absorption by pH level in the absence of TPM. In a related set of experiments,³⁷ Schievelbein *et al* examined the effect of pH on the physiological response to nicotine as measured by blood pressure and found that values were substantially greater at higher pH levels. They also found that pH was the only variable that significantly affected blood pressure in a multivariable analysis of variance that controlled for other factors in the experiments, including the specific dogs and the order of testing (in a previous experiment, the first test on an animal elicited a more dramatic response than did subsequent tests). In summary, the results from this series of dog experiments were consistent with the findings of Armitage and Turner.³⁵

Dialysis membrane model studies

Findings from the FDA's National Forensic Chemistry Center are consistent with the animal studies.²⁴ These studies examined the rate of nicotine absorption across a dialysis membrane to simulate absorption across human oral mucous membranes. In testing numerous brands of smokeless tobacco products, three main factors in governing the rate of nicotine transfer were identified: (a) the total amount of a given brand of smokeless tobacco; (b) the presence or absence of a teabag-like "pouch" to contain the tobacco; and (c) the pH of the product. Increased quantity or pH of the tobacco resulted in increased nicotine absorption. Tobacco marketed in pouches released its nicotine more slowly than did the same tobacco removed from its pouch. These factors interact to alter the amount of nicotine obtained by consumers under conditions of typical use. Consistent with the idea that pH primarily affects the speed of absorption, the maximal difference between high-pH and low-pH products in the amount of nicotine transferred across the membrane was seen in the first two minutes of administration. For example, after two minutes the typical dose of 1.5 g of a high-pH product known as a product for experienced users had delivered 12 times more nicotine than the standard 0.5 g

pouch-contained dose of a low-pH product that was marketed to novice users; by 10 minutes post-administration, the dose differential was less than threefold.

Results from a recent in-vitro study,³⁸ conducted using samples of porcine mucosa and skin, are consistent with those of the FDA's National Forensic Chemistry Center.²⁴ Nair *et al* reported that higher permeation rates across both mucosa and skin were obtained for un-ionised nicotine than for ionised forms. Specifically, they concluded that permeation rates across both cutaneous and mucosal tissues increase exponentially with increasing pH of the nicotine solution. Nair *et al* attributed this effect to the increased amount of un-ionised nicotine and lower amount of ionised nicotine at higher pH levels.

Human studies

Data collected by laboratories supported by the US National Institute on Drug Abuse,²² the National Cancer Institute,²³ and two run by the FDA²⁴ have shown that the pH of smokeless tobacco products varies widely, with lower pH products represented by brands that are heavily marketed to inexperienced users, and higher pH products by those marketed to experienced users.^{24 27 31} Furthermore, data from the CDC indicate that young people are twice as likely to switch from low-pH products to high-pH products as to change in the opposite direction.³⁹ In short, these findings support the conclusion that manipulation of the pH of smokeless tobacco is a major, if not the primary, means by which manufacturers control the nicotine-dosing characteristics of their smokeless tobacco products and thus promote addiction to them among young users.

Few studies have directly investigated the effects of pH on the absorption of nicotine from smokeless tobacco products, although several studies support the findings of the animal investigations. In summarising the available data at the time of their review, Beckett and Hossie⁴⁰ noted that the oral mucosa behaves similarly to other biological lipidal membranes relative to its penetration by drugs: the drugs must be in solution to be absorbed; un-ionised, lipid-soluble compounds are rapidly absorbed; and ionised lipid-insoluble compounds are not well absorbed. In-vivo experiments with basic drugs (including (-)-nicotine) showed that the buccal absorption rose with increasing concentration of the un-ionised form. They concluded that the amount of drug absorbed depended on its pKa, the rate of partitioning of the un-ionised form of the drug, the lipid-water partition coefficient, and the pH of the solution. In a subsequent study, Beckett, Gorrod, and Jenner⁴¹ examined the buccal absorption of various tobacco alkaloids and found a strong effect of increased pH on absorption of nicotine—virtually none was absorbed at pH 5.5, about 10% at pH 7, and more than 30% at pH 9. Ivey and Triggs⁴² found a similar pattern for absorption of nicotine from the stomach; essentially none was absorbed at

pH 1, absorption was increased at pH 7.4, and nicotine was well absorbed at pH 9.8.

In a small Swedish study ($n = 54$), Andersson, Bjornberg, and Curvall compared the uptake and metabolism of nicotine in users of loose *snus* (oral moist snuff), portion-bag *snus*, and chewing tobacco.⁴³ These investigators analysed the nicotine content and pH level of the products and estimated the systemic dose of nicotine by measuring the nicotine and metabolites excreted in the urine in 24 hours. They concluded that users of chewing tobacco had a higher systemic dose of nicotine than users of *snus*, despite an acidic pH of 4.9 for chewing tobacco and alkaline pH values of 7.9–8.2 for portion-bag *snus* and pH 8.5–8.6 for loose *snus*. However, this study did not compare absorption characteristics for products differing in pH on a gram-for-gram basis. It also did not provide any data on the rate of nicotine absorption following administration of a smokeless tobacco dose. The fact that the total nicotine content of the chewing tobacco brand in this study was much higher (21.2 mg/g) than for loose (8.6–9.1 mg/g) or portion-bag *snus* (9.0–10.3 mg/g) also lessens the study's import, as does the researchers' reliance on urinary output of nicotine and its metabolites only to estimate systemic dose with no confirmatory blood levels. Thus, if some of the nicotine present in the saliva was swallowed, both the swallowed nicotine and its metabolites might eventually be detected in urine. Because the stomach is acidic (that is, has a low pH), little nicotine would be expected to be in the un-ionised state or to be absorbed from the gastric mucosa.^{33–35} Thus, ionised nicotine that was extracted from the tobacco and swallowed will still enter the gastrointestinal tract, undergo metabolism in the liver, and be excreted in the urine.^{1 44} Because of the differences in the pharmacology of un-ionised and ionised nicotine, the differences in systemic dosage calculated by Andersson, Bjornberg, and Curvall⁴³ do not necessarily translate into differences in pharmacologically meaningful dosages.

In contrast to the conclusions reached by Professor Idle in his document supplied to UST, a review on which he was a co-author⁴⁵ notes that pH differences throughout the body determine the amount of nicotine absorbed. It also observes that the buccal mucosal absorption of nicotine from tobacco smoke depends strongly on the pH of the smoke. In addition, the review states that nicotine absorption from chewing tobacco and nicotine gum is facilitated by buffering the preparations to an alkaline pH of ~8.5. All of these statements support the FDA's conclusions that manufacturers buffer chewing tobacco and oral snuff products to an alkaline pH to enhance nicotine absorption.²⁴

Epidemiological evidence

Evidence from an American epidemiological study also supports the importance of pH levels for nicotine absorption. In this study,³⁹ adolescent and young adult users of smokeless tobacco cited difficulty in quitting, which is a

symptom of addiction, as one reason for using a particular product. After controlling for frequency and duration of use, the researchers found that persons who used Kodiak or Copenhagen moist-snuff brands were about twice as likely as users of Skoal Bandits or Skoal to report difficulty quitting as a reason for use; Kodiak and Copenhagen users were also more likely to report one or more symptoms of the nicotine withdrawal syndrome on previous attempts to quit. This pattern is consistent with the levels of un-ionised nicotine for these brands and their relative absorption through the oral mucosa as predicted from their measured nicotine content and pH levels.^{22 23} Specifically, both Kodiak and Copenhagen have been classified as high or very high nicotine delivery systems, and Skoal Bandits as a low nicotine delivery system; most other varieties of Skoal are thought to deliver moderate to moderately high levels of nicotine.^{22 23}

Nicotine replacement therapy studies

Several studies of nicotine polacrilex gum, which became available in the 1970s to treat nicotine dependence, have illustrated the connection between pH and nicotine dosage. For example, the 1977 report of Axelsson and Brantmark⁴⁶ compared the use of 4-mg pieces of nicotine gum buffered with sodium carbonate and bicarbonate to increase salivary pH level with 4-mg pieces without these agents; it found that peak blood nicotine levels in subjects using the buffered gum were two and a half times higher than in those using the unbuffered gum (10 ng/ml *vs* 4 ng/ml). Unbuffered gum was also less effective than the buffered gum in preventing withdrawal symptoms, which suggests that the increase in the level of un-ionised nicotine increased the pharmacological nicotine dosage. More recently, Henningfield *et al*⁴⁷ examined the effect of acidic beverages on absorption of nicotine from nicotine polacrilex gum and found that rinsing with cola (mean pH 2.57) or coffee (mean pH 5.24) virtually eliminated the absorption of nicotine, but rinsing with distilled water did not seem to block this process at all. These experiments confirmed that the pH of the oral environment, and not merely rinsing, can control the absorption of nicotine through the oral mucosa.

Two other studies conducted at the National Institute on Drug Abuse examined the effects of oral manipulation (gum chewing rate)⁴⁸ and duration of oral exposure (controlled by expectorating at intervals ranging from 6 to 96 s)⁴⁹ on nicotine absorption from nicotine polacrilex gum that was buffered to produce a pH level of approximately 8.0. Neither study found an appreciable effect.

Researchers who were developing an oral capsule for delivering nicotine (to study its physiological effects) observed that higher pH levels yielded greater absorption of nicotine.⁵⁰ Specifically, they found that by increasing the concentration of the alkaline buffer in a gelatine capsule containing 4 mg of nicotine,

they were able to increase the peak nicotine plasma levels from 4–10 ng/ml to 10–15 ng/ml.

Because it is physiologically similar to oral mucosa, absorption through the skin might be expected to be affected by pH levels as well. One in-vitro study of nicotine penetration through skin in transdermal nicotine delivery systems⁵¹ found a 10-fold higher skin nicotine penetration with a vehicle buffered to pH 10 than in vehicles with pH 4.

Tobacco industry documents

Internal documents from British-American Tobacco (BAT) that recently became publicly available provide evidence that the tobacco industry conducted research on pH buffering and nicotine absorption as early as 1968. In a series of in-vitro experiments, BAT researchers found that the pH of the solution controlled the rate at which nicotine diffused through selective synthetic and natural membranes.⁵² The author concluded: "The rate at which nicotine is absorbed into the blood stream from the mouth appears to be largely controlled by the pH of the saliva in the mouth." In reviewing several published studies, another BAT internal report⁵³ noted that nicotine in cigar smoke (pH 8.5) was absorbed more readily through the oral mucous membranes than was nicotine in cigarette smoke (pH 5.3). They attributed this finding to the higher concentration of un-ionised nicotine in the relatively alkaline cigar smoke. They also noted that dogs absorbed much more nicotine administered orally when the nicotine solution had a pH of 10.2 than when its pH was 7.4.

In a document describing the additives used in snuff manufacturing, the Swedish Tobacco Company has indicated that it controls nicotine dosage by controlling the pH level.⁵⁴ They describe one product additive as "sodium carbonate (Na₂CO₃) which increases the pH-level, which makes nicotine more easily released from the tobacco and subsequently facilitates the uptake of nicotine through the mucous membranes of the mouth. The sodium carbonate is altered in the snuff into bicarbonate" (translated from the original Swedish).

Other evidence

That pH affects mucosal absorption in some way has been demonstrated in animal and human models for a number of basic drugs other than nicotine, as well as for a number of acidic drugs. Travell³³ demonstrated that cocaine, strychnine, and atropine sulfate were all absorbed more readily in laboratory animals when the pH was raised to more alkaline levels. In addition, relationships between pH and absorption have been demonstrated in humans for amphetamine, methylamphetamine, benzphetamine, fenfluramine, methadone, ephedrine, pseudoephedrine, and other alkaline drugs.⁵⁵ Because many drugs are passively absorbed across buccal mucosa (there is no specialised transport system) and absorption increases with the concentration of the un-ionised form, acidic drugs would be

expected to be absorbed more readily in an acidic environment. This was empirically demonstrated for *p*-alkylphenylacetic acids, phenylacetic acid, *p*-chlorobenzoic acid,⁴⁰ and salicylic and benzoic acids.⁵⁶

Conclusions

Animal studies, an experiment using a dialysis membrane model, and human studies using a variety of nicotine-delivering products have shown that pH is a major determinant of nicotine absorption across mucosal tissues. Findings consistently demonstrate that raising the alkalinity of the aqueous solution of nicotine increased both its physiological effects and measured blood levels. Evidence from humans, although more limited than that from animals, generally supports this conclusion. For example, experiments using nicotine polacrilex gum consistently found that a more alkaline pH enhances nicotine uptake. A recent epidemiological study found that symptoms of nicotine addiction and withdrawal were more likely among persons using moist snuff brands with higher pH levels and higher levels of un-ionised nicotine than among those using brands with lower pH levels.³⁹ One study conducted with smokeless tobacco users did not find the same pattern but suffered from methodological problems.

There is limited information on the effects of behavioural and biological factors on oral absorption of nicotine from smokeless tobacco. The available data suggest that, compared with the pH of the product, the rates of expectoration and oral manipulation probably have little effect on the rate of nicotine absorption. Nicotine dosage from smokeless tobacco may be affected by factors such as the presence of a teabag-like pouch (which may be used by manufacturers to further control the rate of nicotine delivery) and the quantity used. The effect of such factors, however, is not central to the issue of whether pH is a determinant of the rate of nicotine absorption from smokeless tobacco.

Taken together, the studies reviewed in this paper support the conclusions of the US Food and Drug Administration²⁴ and others²⁷ that control of pH is an important means by which manufacturers of smokeless tobacco control the speed of nicotine delivery of their products. The findings of this review also support the request of the Office on Smoking and Health that manufacturers of smokeless tobacco provide brand-specific information on the pH of their products.

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