The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.

MEMORANDUM

FROM: Todd L. Cecil, Ph.D.
Chemist
Division of Product Science, Office of Science

Todd L. Cecil -S Digitally signed by Todd L. Cecil -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Todd L. Cecil -S, 0.9.2342.19200300.100.1.1=2001734216
Date: 2016.05.02 07:11:34 -04'00'

THROUGH: Tim M. Brewer, Ph.D.
Team Leader
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Matthew Holman, Ph.D.
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Date: 2016.05.02 07:40:53 -04'00'

TO: David L. Ashley, Ph.D.
Director
Office of Science

SUBJECT: Dissolution as a Critical Comparison of Smokeless Product Performance: SE Requirements and Recommendations for the Review of Dissolution Studies

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Purpose

The purpose of this memo is to recommend the addition of a dissolution requirement for the SE determination of smokeless products. The recommendation includes the conditions under which dissolution results should be requested, the manner in which the dissolution results could be reviewed, and what they would tell us about the products.

Introduction

It is estimated that 3.5% of U.S. adults and 6.1% of high school students are current users of smokeless tobacco products [1]. These products are designed to be held in the mouth and allowed to release nicotine over time. The rate of the nicotine release is controlled through a number of mechanisms, including addition of pH modifiers [2, 3], pouch materials [2, 3], casing and dressing components (such as fillers and binders) [4-6]. The rate of nicotine release can be modified by a number of physiological factors, including salivary flow, salivary pH changes, oral enzymes and other factors [7-9].

Manufacturers have stated that the pH changes in their products don't make large changes to the pH of the saliva because of the buffering capacity of saliva. However, studies have demonstrated that these claims are without merit [10, 11]. The Ciolino study indicated that "the

acid-base buffering capacities … of moist snuff products were determined to be 10-20 times higher than the acid-base buffering capacity of unstimulated, whole human saliva". The Bardow study indicates that the typical buffering capacity of human saliva is approximately 8.9 mM at a pH of 6.8 in unstimulated whole saliva and 13.5 mM at a pH of 7.2 in stimulated whole saliva. The buffering capacity is provided largely by a combination of carbonate and phosphate buffers. The Bardow study also states that an unstimulated salivary flow rate is 0.55 mL/min and a stimulated salivary flow rate is about 1.66 mL/min. Further studies have shown that the typical session length for moist snuff is approximately 39.9 minutes [12]. Therefore, a stimulated salivary condition would lead to a total salivary output of 66 mL and therefore approximately 0.896 mM of total buffering capacity, while an unstimulated salivary condition would yield a total flow of 22 mL and 0.195 mM of buffering capacity. However, total salivary output is not representative of the total salivary exposure to which a tobacco product would be exposed. In their 1995 study, Sivarajasingam and Drummond demonstrated that approximately 30 percent of total salivary output was provided by the minor salivary glands in the buccal regions[13]. Thus, total salivary exposure of a tobacco product inserted into one of the four buccal pockets could limit product exposure in the range of 5.5 – 16.5 mL, depending upon level of stimulation at the site of nicotine exposure. At these volumes, an addition of a strongly basic pH additive (ammonium chloride or ammonium carbonate) would saturate the buffering capacity at a concentration of 2.5 – 10 mg/g of tobacco product. Small additions (as little as 1 μg) in excess of this capacity would yield changes in local pH[1]. Further, the addition of mucoadhesives (such as guar gum, acacia (gum arabic), or hydroxypropylcellulose) create a "hydrogel" effectively isolating the tobacco product from much of the larger salivary effects [4, 14, 15] thus increasing the effects of pH adjustment changes in the local environment of the gel.

The complexity of salivary flow, composition, and the complex interactions of the tobacco product additives and buccal saliva will directly affect the nicotine release in the buccal cavity, making it difficult to predict the nicotine release patterns for new products or to predict the result of changes to components of new products as part of the evaluation of significant equivalence without some form of measurement. While *in-vivo* measurement of nicotine release is possible, the costs and variability of obtaining this type of information precludes its use as an ongoing product comparison measure. However, the effects of individual component changes and changes to product design can be measured using dissolution procedures similar to those used for nicotine gums and tablets used for smoking cessation [3, 16]. The results from dissolution testing cannot be used as direct measures of levels to which individual users are exposed, but they can be effective at providing insight into product performance and relative differences in the likely experience of users in general[17]. The goals of this memorandum are to recommend a performance test for smokeless tobacco in the same manner that cigarette smoke is tested to assess the performance of cigarettes. In addition, this memo intends to provide recommendations on when performance testing should be requested, who should review the results and how to evaluate the results of performance testing.

Background

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[1] Once the buffering capacity has been exceeded, an excess of 0.1 mg of ammonium chloride would adjust the saliva in the buccal cavity by 3 – 3.4 pH units or about 2 pH units for the total salivary output.

Cigarette tobacco is a dried and often coated natural product that contains nicotine and a variety of other constituents present in plant materials. In the 1960s, researchers began to examine the smoke emitted from the combustion of cigarettes [18]. The gold standard for the comparison of cigarettes includes the measurement of ingredients in the cigarette and the products of their combustion. These two types of testing, often termed, "product" and "performance", respectively, are very different. Where the results of the testing differ, the performance tests (smoking results) typically carry the greater weight in determining the potential health effects to the users of the tobacco products. While the performance test for cigarettes is well-developed and standardized, smokeless products do not have an equivalent test.

Performance Tests

There are five major types of smokeless tobacco products sold in the United States: moist snuff, dry snuff, loose-leaf chewing tobacco, snus, and dissolvables. Snuff is a finely ground tobacco product that is sold either as moist, dry or packaged in a pouch (sachet). Snuff users typically place a pinch (dip) of the tobacco product in the buccal cavity between their gum and lip, where tobacco chemical compounds are absorbed through the oral mucosa. With many varieties of snuff and chewing tobacco, the user spits out saliva generated during tobacco usage. Some exceptions to this practice are snus and dissolvable products. These products, like the traditional smokeless products, are formulated to produce a specific release rate of nicotine and other constituents such as flavorants. Smokeless product performance is based on solubility rather than volatility to the constituents. In these products, the solvation of nicotine, and other constituents, is the rate-limiting step. In cigarettes, nicotine is in both the free-base and charged form and there are multiple mechanisms by which it can be transferred to the lung cellular membranes [19]. Free-base nicotine, which is the most volatile form, is also the most soluble form and the most rapidly absorbed form of nicotine across all mucosal boundaries [20]. Free-base nicotine is readily absorbed through the oral mucosa and any free-base nicotine that does not have ready access to the mucosa may be swallowed and absorbed through the gastrointestinal (GI) tract. The conversion of mono-protonated nicotine to the free-base form occurs at the pKa of about 8.02[21]. Smokeless products are often formulated with additives that maintain the pH of the tobacco product near that of the pKa at the surface of the tobacco plant material. This provides a rapid release of nicotine to the user. However, much of the nicotine present in the tobacco bulk is present in the monoprotonated form and is bound within the cell walls of the plant[22]. However, upon solvation, the equilibration process of monoprotonated to free-base nicotine occurs rapidly. Therefore, the performance of a smokeless product should involve a rapid onset with a slower equilibration and extraction process, akin to an extended release drug product. This process and the extraction of nicotine over time in the human mouth is a complex process that has not been fully examined. However, the main effects of nicotine exposure have been exploited in the design of smokeless products. The rate of release of nicotine (in the form of free-base nicotine) is a critical design parameter of all tobacco products, but unlike cigarettes, smokeless products have not been extensively measured in the literature [3, 16].

For smokeless products, a faster release rate will more closely approximate the nicotine release of a cigarette, which release nicotine to the brain in about 10 seconds [4] and reach a maximum within 15 minutes [23]. The size of that initial dose and duration of ongoing release will affect the appeal of the product. However, a large initial dose also carries a variety of bodily reactions

including an adrenal spike, dopamine release, and for inexperienced users, dizziness and nausea [24]. The later effects can be mitigated by a slower release rate which may make the product more attractive to beginning users. Because the nicotine release from a tobacco product is so important to the acceptability of the user, it may be useful to consider a nicotine performance test as a target for comparing new and existing products. However, *in-vivo* studies are expensive and introduce physiological and behavioral variables into the evaluation of the tobacco products. Therefore, an *in-vitro* procedure is desired.

Traditionally, the nicotine release from a tobacco product has been modelled using the Henderson-Hasselbach Equation (HHE) to approximate the amount of free nicotine that is available at a point in time based on the pKa of nicotine and the pH of the solution, as a form of *in-vitro* measure. However, the HHE does not fully describe the rate of release from a complex tobacco product. The complexity of smokeless tobacco products is partially attributed to the ingredients (excipient) used in their manufacture, the pH of the oral cavity and formulation, the release of nicotine from the tobacco leaf matrix, and the portion of the tobacco product that is swallowed and undergoes absorption in the small intestine as opposed to the oral mucosa [23]. Further, smokeless formulations may increase in complexity with the addition of fillers, excipients and binders like acacia, guar gum, microcrystalline cellulose, pre-gelatinized starch, and other common pharmaceutical excipients [6, 25]. These excipients provide the physical form, stability, and control the release of nicotine of the formulated product. For example, studies have shown that nicotine blood levels of dissolvable products have a lower maximum blood concentration and a slower initial increase than traditional smokeless tobacco indicating different release characteristics [26]. These differences indicate that the nicotine release is a critical variable for all smokeless products. Due to the similarities between the physical form and action of the dissolvable tobacco products and pharmaceutical products, the well-developed approaches to measure drug release used in pharmaceuticals should apply. Similarly, traditional smokeless products resemble herbal pharmaceutical products with associated release considerations. In each case, the pharmaceutical and herbal industries have increasingly turned to "dissolution" testing as the most applicable *in-vitro* approach. Typical dissolution studies are based on a stirred acid solution intended to loosely resemble the stomach. This very simple dissolution model is generally acknowledged not to be a truly representative human model and is best used as a quality control tool. Specialized dissolution models have also been developed that are more representative of buccal and sublingual drug delivery. Attempts to increase the "bio-relevance" of dissolution of both stomach-centric and buccal-centric models have led to the development of simulated biological fluids (media) [27] and innovative measurement procedures (apparatus) [2]. Regardless of the dissolution model being utilized, there are three criteria that need to be considered when developing a dissolution study, 1) dissolution apparatus and settings 2), dissolution media (pH and additives), and 3) the analytical procedure.

Dissolution apparatus

There are several dissolution apparatus that have been reported to measure buccal delivery (see Appendix A for description[2]), and they include;

- USP Apparatus 4 [6],

[2] Please note that the descriptions show a single dissolution station. The major of dissolution apparatus on the market combine 6 or more stations to allow the replicates necessary for the evaluation of dissolution results.

- European Pharmacopeia Chewing gum Drug Release Apparatus B [28, 29]
- Other novel apparatuses [2, 17, 30].

Each dissolution apparatus has variables that can be adjusted to increase or decrease the sensitivity of the dissolution method. These adjustments may include; media volume, media temperature, flow rate, dip rate, jaw distance, hold times, sampling times, sampling location, among many others. The manipulation of these variables and the content of the dissolution medium are used to adjust the dissolution profiles of sample products to achieve the ability to differentiate formulations of tobacco products. The dissolution apparatus, medium, and sampling details are generally developed by the manufacturer in pharmaceutical applications and the applicability and validity of the procedure is evaluated by the FDA as part of the application process. With tobacco products, the chewing gum machines and Apparatus 4 are both standardized commercially available approaches that should provide acceptable dissolution results for smokeless products. The chewing gum machine would be the most applicable for loose product and those that require mastication for release (chewing tobacco, chewing gums and dissolvables). The chewing gum machines will also work well with portioned products. Apparatus 4 is best suited for portioned products and dissolvable tablets and lozenges. Apparatus 4 is not well suited for loose products (because it is too aggressive and will present too large a surface area as the tobacco pieces float around in the media) or those requiring mastication.

Dissolution media

In addition to determining the appropriate dissolution apparatus, the dissolution media must also be considered. The dissolution media in a traditional pharmaceutical test are aqueous, sometimes with a buffered pH, and occasionally with enzymes like lipase [27]. The choice of dissolution medium, the pH, and the use of enzyme will need to be considered in such a way that the results have some relation to the human physiology. Studies in the literature have shown that bio-relevant dissolution media can be used to develop a strong *in-vivo/in-vitro* correlation (IVIVC) [12,13,14]. In addition, human analog/biorelevant medium (simulated saliva) pH can be changed to more closely model the human changes over the course of a measurement [31]. There are standards for simulated saliva in the *USP-NF* that describe which enzymes to use, when to use them, and what concentrations are most appropriate along with reported analogs [32]. However, unless an IVIVC is sought, a true human analog is not necessary.

Dissolution data are generally presented in two ways. The first is a plot of the percentage released vs time. The percentage released is calculated relative to the t^{∞} time point. For drug products, the percentage release is often measured relative to the labelled value of the product or relative to the assayed content. For tobacco products, both the amount of tobacco used in each measurement and the amount of nicotine present in the tobacco leaves are not known. Therefore, the measurement of individual t^{∞} should be completed for each dissolution run. The second presentation of dissolution data is the individual measured values for each data point in each curve. The dissolution procedures are generally compared using the f_2 comparison equation [33].

$$\text{Equation 1: } f_2 = 50\ \text{LOG}\left([1 + (1/n) \sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\right)$$

Equation 1 - Where n is the number of dissolution sample times, R_t and T_t are the individual or mean percent dissolved at each time point, t, for the reference and test dissolution profiles, respectively. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar [33].

While sampling times are generally developed by the manufacturer, each dissolution curve should include no fewer than 5 data point (time points) with no more than 2 data points needed after the curve plateaus. The majority of the time points should be collected during the initial rise (see Figure 1). Once the plateau is reached, all useful information about the release characteristics of a product have occurred.

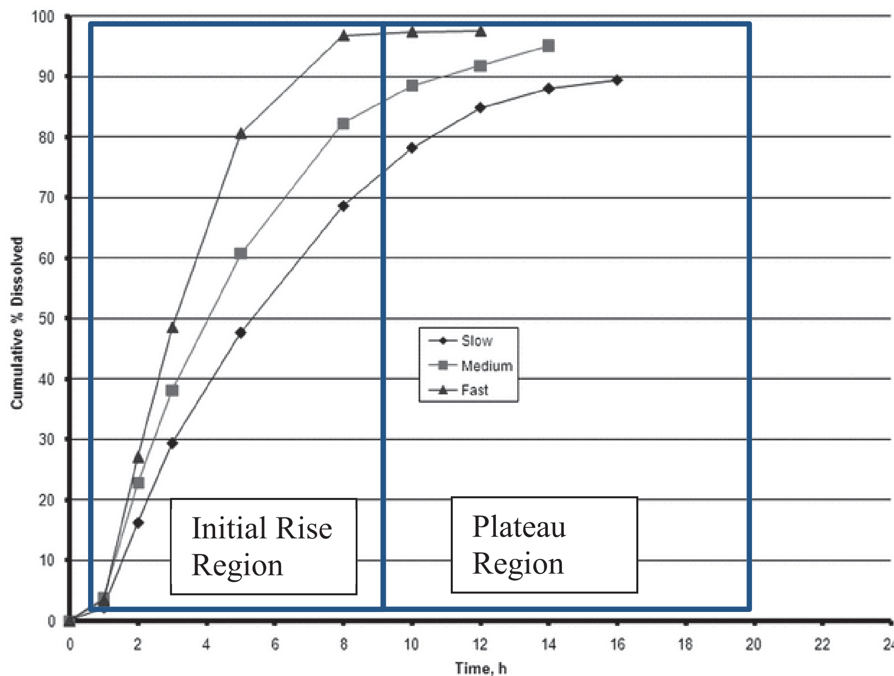

Figure 1. Typical Dissolution Curves of Extended Release Dosage Forms [32]

Figure 2 presents a selection of the dissolution curves for the products presented in the Li paper. The paper uses an alternative dissolution apparatus to collect dissolution profiles for over 20 snus and moist snuff products. This dissolution apparatus shows promise, but is not standardized or commercially available, limiting the ability to repeat this work. However, the results of this procedure can be used as an example of the types of dissolution curves that are expected of smokeless tobacco products. The results clearly differentiate between similar products (i.e. A2 and A3 or B2, B3, and B5) and show the need to collect data points at numerous time intervals until the data plateaus. The majority of the data points should be collected in the first 20 minutes, but due to the relatively slow rise, 30 minute time points are also useable. Many of these curves (J1 and G3 for example) would have benefited from time points prior to 5 minutes.

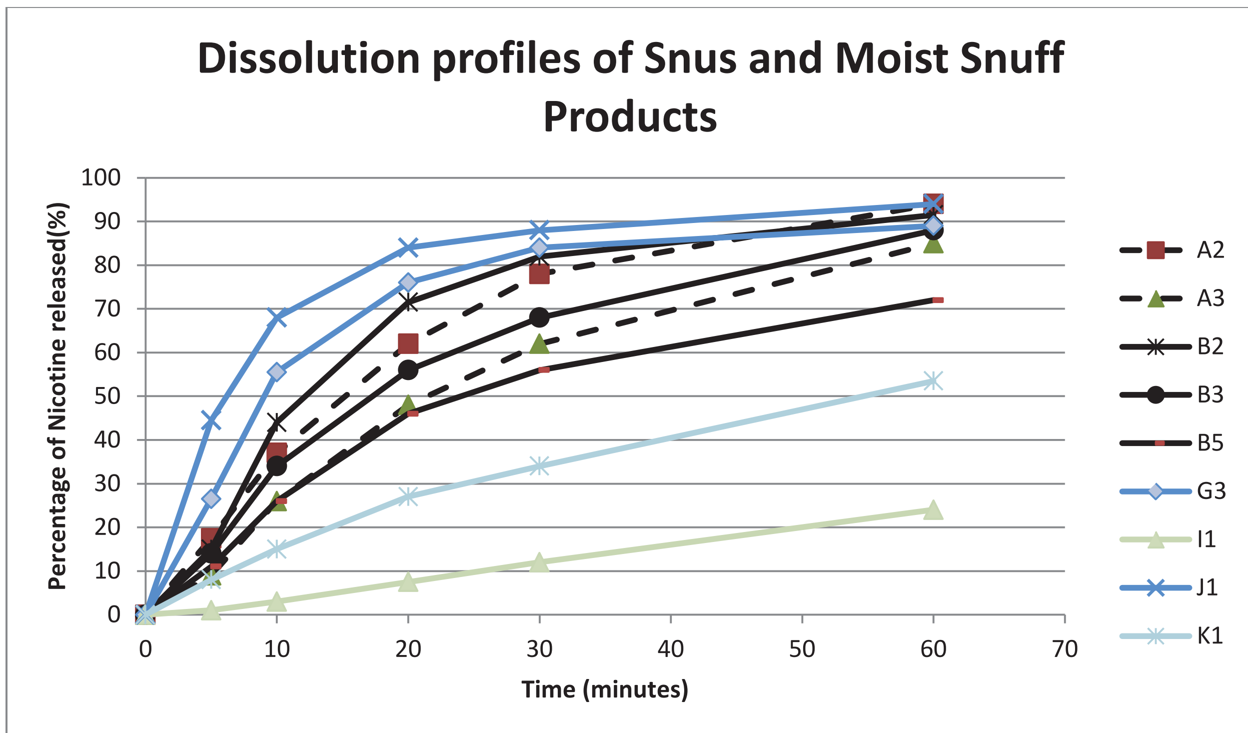

Figure 2. Dissolution profiles of Snus and Moist Snuff Products [2]

Analytical procedure

After each sampling step, the dissolution media must be filtered and the filtrate measured for the nicotine. The filtration step should be completed immediately after sampling to remove any particulate that may contain nicotine from the analytical samples. If filtering is not complete, the nicotine content may increase while waiting to be measured. A critical consideration in the application of an analytical procedure to dissolution samples includes an appropriate solution stability study of the dissolution samples. The length of the analytical determination will need to be considered, because dissolution samples will be time critical and numerous. There are a number of analytical procedures that may be used, ranging from UV determination of the solution (typically the fastest) to HPLC procedures (often the slowest). The analytical procedure should be capable of measuring the analyte in the presence of the media additives and other extracted forms of smokeless tobacco and provide valid, repeatable results across the entire concentration range expected from the dissolution study.

Recommendation

Examples for when dissolution studies may be requested include the following differences exist between the new and predicate products:

- Change in the pH additives [34]
    - A change from Ammonium Chloride to Ammonium Carbonate effectively doubles the amount of ammonia added to the and shifts the buffer capacity

    - The addition of salt counter ions increases the buffering capacity, thus extending the period of high pH conditions and shifting the release rate by shifting the equilibrium equation and extending the fast release portion of the nicotine release curve.
- Change in the pH of 0.1 or greater [34]
    - Depending upon the predicate product pH, a change to pH of 0.1 units can have a large impact according to the HHE. However, manufacturers have stated that the pH changes don't make large changes. The presentation of a nicotine dissolution curve will either support their position or that of the HHE.
    - A shift to the pH can have myriad effects on release rate depending upon; additives, tobacco type, buffer capacity, and engineering factors (cut width, length, pouch materials, etc)
- Addition of Binders, Fillers, or Accelerants [35]
    - Guar Gum, Acacia (Gum Arabic), Magnesium Stearate, Xanthan Gum, Sodium alginate, Carrageenan, Chitosan, Pectin, Polyethylene oxide, Ethylcellulose, Cellulose Acetate have all been used to inhibit the dissolution rates.
- Change in Tobacco Cut Size [34]
    - A major factor in the availability of bulk nicotine and time necessary to effect the equilibration constant is surface area of the bulk tobacco leaves in the product. Enhanced surface area may also increase the release rate.
- Changes in the Pouch Materials of Portioned Smokeless Products
    - The permeability of the pouch material may affect the microenvironment within the pouch. Lower permeability may drive the conversion of nicotine to free nicotine.

Proposed Boilerplate Deficiency Language

All of your SE Reports describe the ingredients, measured nicotine values, and target pH values of your new and predicate products. Your SE Reports indicate [include as appropriate, a change in the pH additives, pH changes, the addition of binders and fillers, a change in the tobacco cut width and length, and a change to the pouch materials (used in the portioned products), between your new and corresponding predicate products]. These changes to the tobacco product can affect the release rate and total nicotine released from the products. In addition to changes in the release rate of nicotine, these changes may change the rate and total amount of HPHCs including [ ]. Provide adequate evidence and scientific rationale that such changes do not cause the new products to raise different questions of public health.

One way to demonstrate that the changes that have been made to the tobacco product do not raise different questions of public health is through the measurement of nicotine and HPHC release rates and total content from the new and predicate products. This information could be obtained through studies of nicotine, [ ] in artificial saliva (using in vitro dissolution experiments) and may provide such evidence. If nicotine release data is provided, include the following:

a. Description of the dissolution apparatus (apparatus type, media volume)
b. Description of the dissolution conditions (media, temperature, stir/flow rate, etc)

c. Description of the dissolution media (pH, buffers, enzymes, buffer capacity, degassing, etc)
d. Description and rationale for the sampling time points (should include 3 time point in initial release period and no more than 2 time points in the steady state portion of the release curve)
e. Description of sample size and disposition (how much is added to the vessel, was a sinker used, etc)
f. Percentage nicotine released relative to a t_∞ for each sample vs time plots for a representative sample of the new and predicate products (t_∞ is determined by increasing the flow rate for a period of time after steady state is reached)
g. Quantitative test protocols and method used
h. Testing laboratory and their accreditation(s)
i. Length of time between date(s) of manufacture and date(s) of testing
j. National/international standards used and any deviations(s) from those standards. If deviation(s) is not the same for methods used for the new and predicate products, provide scientific evidence demonstrating that the testing result for the new and predicate products are accurate and comparable.
k. Number of replicates
l. Standard deviation(s)
m. Complete data sets
n. A summary of the results for all testing performed
o. Storage conditions prior to initiating testing

References

1. Arrazola, R.A., et al., *Tobacco Use Among Middle and High School Students-United States, 2000-2009 (Reprinted from MMWR, vol 59, pg 1063-1068, 2010).* Jama-Journal of the American Medical Association, 2010. **304**(23): p. 2586-2588.
2. Li, P., et al., *A novel model mouth system for evaluation of In Vitro release of nicotine from moist snuff.* Chem Cent J, 2013. **7**(1): p. 176.
3. Nasr, M., J.C. Reepmeter, and Y. Tang, *In Vitro Study of Nicotine Release from Smokeless Tobacco.* Journal of AOAC International, 1998. **81**(3): p. 540-543.
4. Ngwuluka, N.C., et al., *Formulation and evaluation of paracetamol tablers manufactured using the dried fruit of Phoenix dactylifera Linn as an Excipient.* Res. Pharm. Biotech., 2010. **2**(3): p. 25-35.
5. Shirwaikar, A., et al., *Herbal excipients in novel drug delivery systems.* Indian J Pharm Sci, 2008. **70**(4): p. 415-22.
6. Bhardwaj, T.R., et al., *Natural gums and modified natural gums as sustained-release carriers.* Drug Dev Ind Pharm, 2000. **26**(10): p. 1025-38.
7. Streckfus, C., L. Bigler, and T. O'Bryan, *Aging and Salivary Cytokine Concentrations as Predictors of Whole Saliva Flow Rates among Women.* Gerontology, 2002. **48**(5): p. 282-288.
8. Sreebny, L.M., *Saliva in health and disease: an appraisal and update.* International Dental Journal, 2000. **50**(3): p. 140-161.
9. Humphrey, S.P. and R.T. Williamson, *A review of saliva: Normal composition, flow, and function.* The Journal of Prosthetic Dentistry, 2001. **85**(2): p. 162-169.
10. Ciolino, L.A., et al., *The relative buffering capacities of saliva and moist snuff: implications for nicotine absorption.* J Anal Toxicol, 2001. **25**(1): p. 15-25.
11. Bardow, A., et al., *The buffer capacity and buffer systems of human whole saliva measured without loss of CO2.* Archives of Oral Biology, 2000. **45**(1): p. 1-12.
12. Hatsukami, D.K., R.M. Keenan, and D.J. Anton, *Topographical Features of Smokeless Tobacco Use.* Psychopharmacology, 1988. **96**(3): p. 428-429.
13. Sivarajasingam, V. and J.R. Drummond, *Measurements of human minor salivary gland secretions from different oral sites.* Archives of Oral Biology, 1995. **40**(8): p. 723-729.
14. Shojaei, A., *Buccal Mucosa As A Route For Systemic Drug Delivery: A Review.* J. Pharm. Pharm. Sci, 1998. **1**(1): p. 15-30.
15. Marani, P.L., G.D. Bloisi, and D.F.S. Petri, *Hydroxypropylmethyl cellulose films crosslinked with citric acid for control release of nicotine.* Cellulose, 2015. **22**(6): p. 3907-3918.
16. Kvist, L.C., et al., *Equipment for drug release testing of medicated chewing gums.* J Pharm Biomed Anal, 2000. **22**(3): p. 405-11.
17. Delvadia, P.R., W.H. Barr, and H.T. Karnes, *A biorelevant in vitro release/permeation system for oral transmucosal dosage forms.* Int J Pharm, 2012. **430**(1-2): p. 104-13.
18. Report, S.G., *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*, P.H.S.O.o.t.S. General, Editor. 1964, Public Health Service Publication No. 1103.
19. Ferris Wayne, G., G.N. Connolly, and J.E. Henningfield, *Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents.* Tob Control, 2006. **15**(3): p. 189-98.

20. Tomar, S. and J.E. Henningfield, *REview of the evidence that pH is a determinant of nicotine dosage from oral use of smokeless tobacco.* Tobacco Control, 1997. **6**: p. 219-225.
21. Lide DR, e., *CRC Handbook of chemistry and physics. 71st ed.* 1990, Boca Raton, Florida: CRC Press.
22. Shitan, N., M. Morita, and K. Yazaki, *Identification of a nicotine transporter in leaf vacuoles of Nicotiana tabacum.* Plant Signaling & Behavior, 2009. **4**(6): p. 530-532.
23. General, S., *Surgeon General Report 1988: http://whyquit.com/CDC/SGR_1988_Chapter_2_Nicotine_Pharmacokinetics.pdf.* 1988.
24. Webcontent, P.T., *Nicotine.* Psychology Today, 2014.
25. Fischer, M. and G. Schepky, *The Effect of Hygroscopic Formulation Ingredients on the Sorption Characteristics of Tablets.* Drug Development and Industrial Pharmacy, 1995. **21**(3): p. 279-300.
26. Kotlyar, M., et al., *Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge.* Tob Control, 2007. **16**(2): p. 138-42.
27. Marques, M.R.C., R. Loebenberg, and M. Almukainzi, *Simulated Biological Fluids with Possible Application in Dissolution Testing.* Dissolution Technologies, 2011. **18**(3): p. 15-28.
28. Brown, W., et al., *Collaborative Study of the Variability of Drug Release Results from Nicotine Gums using Two Apparatus Designs* Pharmacopeial Forum, 2015. **41**(1).
29. Gajendran, J., J. Kramer, and S.R. Knudsen, *Product Performance Test for Medicated Chewing Gums* Pharmacopeial Forum, 2008. **34**(3).
30. Rachid, O., et al., *Dissolution testing of sublingual tablets: a novel in vitro method.* AAPS PharmSciTech, 2011. **12**(2): p. 544-52.
31. Klein, S. and J.B. Dressman, *Comparison of Drug Release From Metoprolol Modified Release Dosage Forms in Single Buffer versus a pH-Gradient Dissolution Test.* Dissolution Technologies, 2006. **13**(1): p. 6-12.
32. USPC, *USP/NF 38/33.* 2015.
33. FDA, *Guidance for Industry: Immediate Release Solid Oral Dosage Forms - Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In-Vitro Dissolution Testing, and In-Vivo Bioequivalence Documentation.* US FDA, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070636.pdf, 1995.
34. Jambhekar, S.S. and P.J. Breen, *Drug dissolution: significance of physicochemical properties and physiological conditions.* Drug Discovery Today, 2013. **18**(23–24): p. 1173-1184.
35. Nokhodchi, A., et al., *The role of oral controlled release matrix tablets in drug delivery systems.* Bioimpacts, 2012. **2**(4): p. 175-87.

Appendix A. Dissolution Apparatus

Apparatus 4 ***(Flow-Through Cell)*** [32]

The assembly consists of a reservoir and a pump for the Dissolution Medium; a flow-through cell; and a water bath that maintains the Dissolution Medium at a specified temperature. The pump forces the Dissolution Medium upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must deliver a constant flow (±5% of the nominal flow rate); the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute. Dissolution test procedures using a flow-through cell must be characterized with respect to rate and any pulsation. The flow-through cell (see Figures 5), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; and a tablet holder (see Figures 5) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath

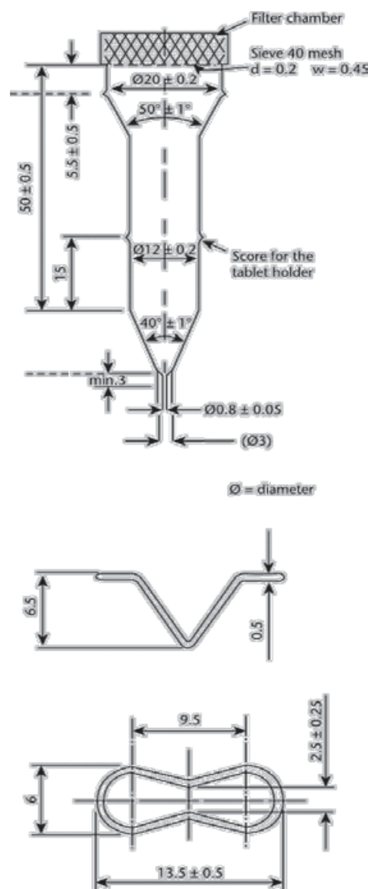

Figure 5. Apparatus 4, small cell for tablets and capsules (top), tablet holder for the small cell (bottom).
(All measurements are expressed in mm unless noted otherwise.)

The apparatus uses a clamp mechanism and two O-rings to assemble the cell. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use suitably inert tubing, such as polytef, with about 1.6-mm inner diameter and chemically inert flanged-end connections.

Chewing Gum Apparatus [29]

One of the noncompendial apparatus commercially available (distributed by Erweka) was designed by Wennergren [16]. The schematic representation of the Wennergren chewing apparatus is shown in Figure 7. The chewing procedure consists of reciprocations of the lower surface in combination with a shearing (twisting) movement of the upper surface that provides mastication of the chewing gum and at the same time adequate agitation of the test medium. The upper jaw has a flat surface that is parallel to the central part of the lower surface. The small brim of the lower surface is angled upwards (45 degrees) so that the lower surface functions as a small bowl with a flat bottom. This bowl prevents the chewing gum from sliding during mastication.

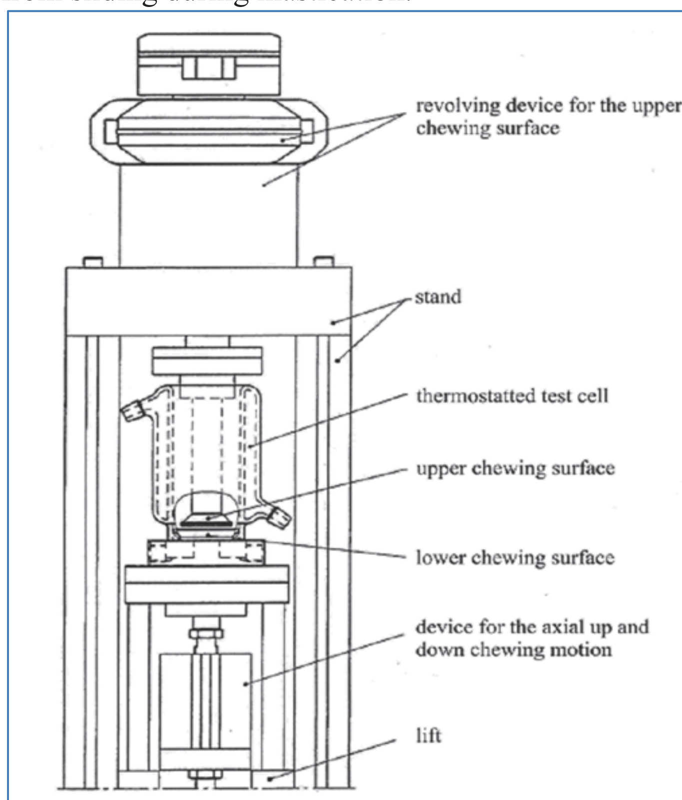

Figure 7. Single-module chewing apparatus from Wennergren

Investigations of the performance of the chewing apparatus with multiple drug products were published by Wennergren et al [16]. The influences of different operational parameters of the chewing gum apparatus on drug release have been carefully investigated [28].