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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: File

From: Mona Shrestha, Ph.D.,
Chemist,
Branch I, Division of Product Science,
Office of Science, Center for Tobacco Products

Digitally signed by Mona Shrestha -S
Date: 2021.09.01 10:37:28 -04'00'

Through: Salome Bhagan, Ph.D.,
Acting Team Supervisor,
Branch I, Division of Product Science
Office of Science, Center for Tobacco Products

Digitally signed by Salome Bhagan -S
Date: 2021.09.01 10:52:43 -04'00'

Matthew J. Walters, Ph.D., M.P.H.
CDR, US Public Health Service,
Deputy Director, Division of Product Science
Office of Science, Center for Tobacco Products

Digitally signed by Matthew J. Walters -S3
Date: 2021.09.01 12:18:43 -04'00'

Subject: Recommended approaches for reviewing nicotine dissolution profile differences for smokeless tobacco products and other orally placed tobacco products in Pre-Market Tobacco Applications.

Background

Differences in smokeless tobacco products (STPs) such as pH additives, tobacco cut size, and pouch materials of portioned smokeless products in a new product compared to a predicate product may impact nicotine release rates and therefore, it may be necessary to evaluate differences in nicotine release between new and predicate STPs to determine if the new tobacco product raises different questions of public health. In SE Reports, dissolution studies of STPs are often used to evaluate nicotine release by approximating the amount of nicotine available at a point in time which can be used to generate a tobacco product's nicotine dissolution profile, Figure 1. The information that can be derived about STPs based on dissolution profiles, how to review dissolution results in SE Reports, and the conditions under which dissolution studies should be requested are captured in the memo: Dissolution as a Critical Comparison of Smokeless Product Performance: SE Requirements and Recommendations for the Review of Dissolution Studies (May 2016)[1]. The purpose of this memo is to expand on the May 2016 memo by providing information on situations in which the predicate and new STPs have similar or different dissolution profiles. Examples of various dissolution profiles are also included to help the chemistry reviewer easily recognize similar and different dissolution profiles. This memo also provides example deficiency language that may be helpful to the chemistry reviewer in writing a review where the new and predicate STP are found to have different dissolution profiles.

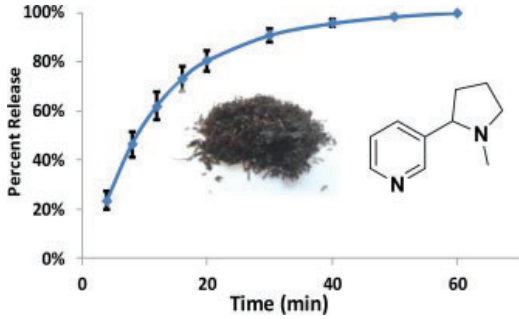

Figure 1. Example of a STP nicotine dissolution profile
(Journal of Chromatography B, 1141, 2020, 122012)[2]

Additionally, although the scope of this memo and the May 2016 memo focus on the SE premarket review pathway, the summary of literature and principles of FDA's current approach to analysis of dissolution testing

for STPs in these memos can generally be applied (1) regardless of premarket review pathway and (2) for oral tobacco products that are used in a similar way to STPs and for which the dissolution testing and associated nicotine release are expected to be similar to that in smokeless products.

Overview of Dissolution Methods Used to Generate Dissolution Profiles

Dissolution profiles provide information on the chemical and design parameter differences between a new and a predicate product. A dissolution profile describes the rate at which a chemical compound is released into the dissolution media which is the kinetic release rate of nicotine from the smokeless tobacco product. Methods used to evaluate dissolution profiles include model independent and model dependent methods.[3] The model independent methods use dissolution data in its native form[3] (i.e., data measured directly from the dissolution). Some examples are f_1 (difference factor) and f_2 (similarity factor)[4], bootstrapped f_2 [5, 6] and multivariate[7] approaches. Model dependent methods are based on mathematical functions that can describe the dissolution profiles and after choosing the most appropriate function, dissolution profiles are analyzed using the parameters derived from the function.[3] Different mathematical functions including the zero–order model, First–order model, and Weibull have been used to obtain the best–fit model.[8,9] To determine which method provides the best mathematical fit to the dissolution data, statistical analysis and factors such as determination of the value of the correlation coefficient (r^2) as obtained through linear regression analysis is used. Additionally, mathematical methods to fit the kinetic measure of nicotine release in solvent media may be concentration dependent or independent. The most commonly used method for dissolution profile comparison is using f_1 and f_2 method. Evaluation of dissolution studies using the f_1 and f_2 method is summarized below.

Evaluation of dissolution studies using the f_1 and f_2 method[4]

Variation of dissolution profiles

Calculation of f_1 known as the difference factor, provides a measure of variation between two dissolution profiles. Mathematically, f_1 is the a "perturbation of the relative error formula" and approximates the percent error between two profiles.

The value of f_1 is 0 when the dissolution profiles are identical and increases proportionally as the dissolution profiles differences increases.

$$f_1 = \left[\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right] X\ 100$$

To calculate f_1, identical dissolution conditions must be used for the new and predicate products, where:

- R_t is the dissolution for the predicate product at time t
- T_t is the dissolution of the new product at time t
- n is the number of time points used to evaluate the dissolution

Closeness of dissolution profiles

Calculation of f_2 provides a measure of the closeness between two dissolution profiles. Mathematically, f_2 is the "logarithmic transformation of the sum of squared error" where the average sums of squares of the difference between two dissolution profiles.

The value of f_2 is 100 when the dissolution profiles are identical and decreases as the dissolution profiles differences increases.

$$f_2 = 50\ X \log\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{n}(R_t - T_t)^2}{n}}}\right]$$

To calculate f_2, identical dissolution conditions must be used for the new and predicate products, where:

- R_t is the dissolution for the predicate product at time t
- T_t is the dissolution of the new product at time t
- n is the number of time points used to evaluate the dissolution

As noted in the evaluation of dissolution studies using the f_1 and f_2 method (described above), it is important that identical conditions are used when comparing dissolution profiles between the new and predicate products. Furthermore, among the limited peer reviewed studies for dissolution of smokeless tobacco products,

apparatuses such as U.S. Pharmacopeia (USP) basket (USP–1), paddle (USP–2), and flow–through cell dissolution apparatus 4 (USP–4) have been utilized in the most recent articles.[2,10,11] Dissolution data for new and predicate products are suitable for comparison only when the studies use identical analytical laboratory methods which could typically be one of the USP methods listed above.

Discussion of Similar and Different Dissolution Profiles

To describe differences in nicotine release between a new and predicate product, the f_1 and f_2 method is often used in SE Reports. Therefore, f_1 and f_2 method is used as an example in this memo to discuss differences and similarities in nicotine release as illustrated by dissolution profiles generated from identical dissolution studies. Determination of the similarity of dissolution profiles for new and predicate products should be evaluated using both f_1 and f_2 because they have been acknowledged to be the current standard for dissolution testing and therefore, provide a comprehensive analyses of the dissolution data.[12] Similar dissolution profiles between the new and predicate products result when f_1 is between 0–15 and when f_2 is between 50–100 which indicates the nicotine release between the new and predicate STP are similar. Nicotine release between the new and predicate STP are different when the values for f_1 are greater than 15 and less than 50 for f_2, see Table 1.

Table 1. Similar and different dissolution profiles based on f_1 and f_2 values

Figure	f_1	f_2	Conclusion
2	0–15	50–100	Similar
3a, 3b	>15	<50	Different
3c	>15	50–100	Different
3d	0–15	<50	Different

Similar dissolution profiles

When f_1 and f_2 values are between 0–15 and 50–100, respectively, the dissolution profiles are considered similar and therefore, the product differences for which the dissolution profiles were submitted are not expected to cause the new product to raise different questions of public health with regard to nicotine release. Additionally, a f_2 value of 50 corresponds to an average difference of approximately 10% between the dissolution profiles at all time points.[13] For example, as shown in Figure 2, a graph showing the percent nicotine released as a function of time for both the new and predicate products at identical sampling timepoints may provide sufficient data to demonstrate the nicotine in the new and predicate products have similar release rates. In Figure 2, all six data points for both the new and predicate products almost overlap with one another. A graph such as the one shown in Figure 2 is most likely to have f_1 and f_2 values within the acceptable ranges (such as $f_1 = 2$ and $f_2 = 89$) and therefore, the new and predicate products are considered to have similar nicotine release dissolution profiles. Similar dissolution profiles do not necessarily overlap with one another for all cases but f_1 and f_2 values (between 0–15 and 50–100, respectively) are used to determine similarity.

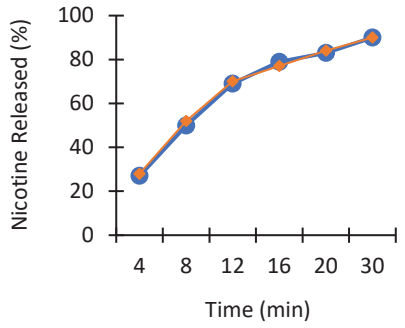

Figure 2. Percent nicotine release of a new product (orange square) compared to the predicate product (blue circle).

Different dissolution profiles

There are various situations using f_1 and f_2 that may result in different dissolution profiles for new and predicate products, see Table 1. Different dissolution profiles indicate there could be a difference in user nicotine uptake with the new product compared to the corresponding predicate product. The dissolution profiles are considered different when one of the scenarios listed in Table 1 for f_1 and f_2 is pertinent irrespective of the nicotine release

rates being higher (Figure 3a) or lower (Figure 3b) for the new product compared to the predicate product. Using dissolution data collected from the same analytical laboratory method to explain differences in dissolution profiles and using the f_1 and f_2 method to generate various examples of dissolution profiles, see Figure 3. As shown in Figure 3, using the f_1 and f_2 method, there can be three scenarios in which the dissolution profiles are different:

(1) f_1 and f_2 are both out of the acceptable ranges (Figures 3a and 3b)
(2) f_1 is out of the range and f_2 is within the range (Figure 3c)
(3) f_1 is within the range and f_2 is out of the range (Figure 3d)

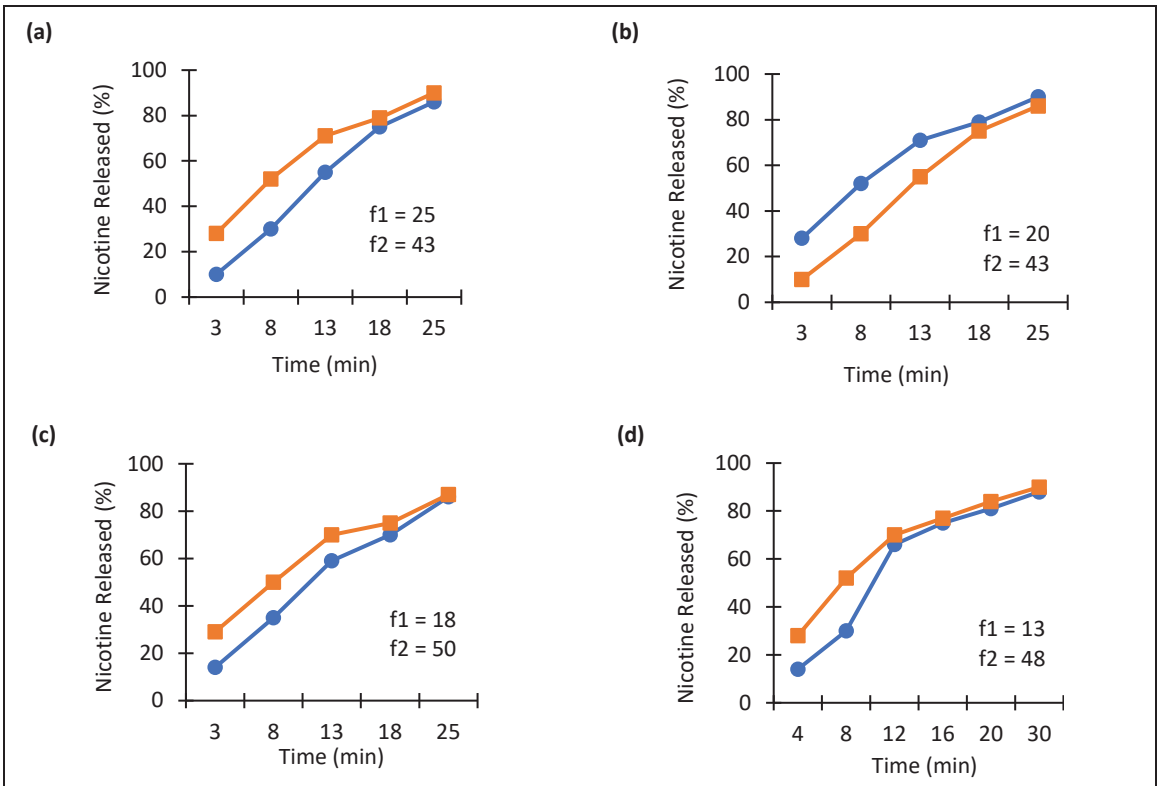

Figure 3 (a – d). Dissolution profiles for new (orange square) and predicate products (blue circle) that are different. Irrespective of whether the dissolution rates are higher or lower for the new product (a and b), the dissolution profiles are different if f_1 or f_2 or both f_1 and f_2 are out of range.

Chemistry findings regarding dissolution testing and data (e.g., dissolution profiles are different, dissolution method is sufficient, etc.) are limited to the chemistry review, but differences in dissolution profiles between a new and predicate product could indicate an impact on user behavior. In this case, the evaluation of user data relevant to user behavior (if included with the application) will be deferred to Behavioral and Clinical Pharmacology (BCP) for further evaluation, but BCP will not further evaluate dissolution testing or data. If the chemistry reviewer determines the dissolution profiles of the new and predicate products are different, additional scientific information such as user data relevant to the evaluation of use and uptake may be included in the chemistry deficiency, on behalf of BCP. An example deficiency is provided in the conclusion section.

Conclusion

Nicotine dissolution profiles may be similar or different. If the dissolution profile of a new product is similar to the predicate product, then the new product would not be anticipated to raise different questions of public health with regard to nicotine release of the new compared to the predicate product. However, for cases where the nicotine dissolution profiles of the new compared to the predicate product are different, i.e., the new

product has a higher or lower dissolution rate compared to the predicate product, the following actions may be appropriate:

1. If user data relevant to the evaluation of product use and uptake is also submitted, the chemistry reviewer should defer the impact on use and uptake of the products based on dissolution to BCP. BCP will determine whether any differences in the submitted user data cause the new product to raise different questions of public health. BCP will not further comment, evaluate, or make conclusions on dissolution data.

2. If user data relevant to evaluation of product use and uptake is not submitted, a deficiency can be included in the Chemistry review. If appropriate, Chemistry will issue the deficiency regardless of whether or not BCP is participating in the review cycle. The deficiency response in any subsequent rounds will likely require BCP evaluation. An example deficiency is found below.

   Example Deficiency

   Your SE Report (All your SE Reports) provided dissolution data examining the percent total nicotine released from the new and (corresponding) predicate products. Evaluation of the dissolution data indicates that the new and (corresponding) predicate products release nicotine at different rates. The different nicotine release rate may affect use of the new product and therefore, user exposure. Provide adequate evidence that the differences in nicotine release between the new and (corresponding) predicate products do not raise different questions of public health. Such evidence could include pharmacokinetic data from a clinical study examining nicotine exposure from the new and (corresponding) predicate products.

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