tablet coating

# Investigation of the relationship between eszopiclone tablet coating and the onset of bitterness perception

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*This article describes a study in which taste panelists examined the bitterness of eszopiclone tablets. The tablets were manufactured with a variety of coatings and coating weights. Dedusting was also considered as a factor in the onset of bitterness. Furthermore, two sensory test methods were used to test bitterness: a lick test and a roll test.*

Eszopiclone tablets, formulated using Opadry II (Colorcon, West Point, PA) film coating, produce an unpleasant taste in 20 to 30 percent of patients. The purpose of the study discussed here was to evaluate the relationship between the film coating and the bitterness perceived during tablet administration, and to determine how coating or process variables affect the time to perceived bitterness. Process variables tested were no dedusting and double dedusting using the standard commercial coating of Opadry II. Coating variables tested were undercoated and overcoated Opadry II, Opadry Taste Mask, and standard Opadry II with an overcoat of Opadry Clear.

This was a two-part study using trained human sensory (taste) panelists who measured the onset of bitterness using a seven-point intensity scale. In Part 1, the face and band of the tablets were separately evaluated following a fixed-sequence, repeated-measures design whereby the panelists licked the test surface and recorded the number of licks to reach moderate intensity bitterness (lick test). In Part 2, tablets were evaluated following a randomized, blinded design whereby the panelists rolled each tablet in the oral cavity and recorded the number of seconds to reach moderate intensity bitterness (roll test).

Mean roll and lick values were highly correlated ($r = 0.94$) and coating variables were significantly different ($p$

< 0.001) in both the lick and roll tests using a repeated-measures Analysis of Variance. Tablets coated with Opadry Taste Mask, overcoated with Opadry II, and coated with Opadry Clear significantly delayed bitter breakthrough compared with non-dedusted, double-dedusted, and undercoated tablets ($p < 0.05$). Tablet dedusting showed no effect on reducing bitter breakthrough.

## Introduction

Eszopiclone, the active ingredient of Lunesta, is a non-benzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. Lunesta is formulated as a film-coated tablet for oral administration and contains 1-, 2-, or 3-milligrams of eszopiclone. For rapid onset of action, the eszopiclone tablets are designed to quickly disintegrate upon ingestion.

As is true of many other active pharmaceutical ingredients (APIs) [1], eszopiclone has an associated unpleasant (bitter) taste. In controlled clinical studies evaluating the safety and efficacy of eszopiclone in adults with insomnia, the frequency of spontaneously reported unpleasant taste in patients taking eszopiclone has ranged from 16.3 percent to 33.3 percent [2, 3]. In one 39-person study [4], this unpleasant taste was correlated to blood and saliva eszopiclone concentrations. However, in larger studies, this correlation to bodily fluids was not preformed, and "unpleasant taste" events were captured without ascribing a specific onset time [5]. Therefore, it remains a distinct possibility that some "unpleasant taste" events from clinical trials occur immediately upon administration of the tablets and that some occur due to the systemic effects of the API.

Bitterness perceived upon tablet administration is hypothesized to occur through two routes. First, in an effort to achieve superior onset times, eszopiclone tablets have been formulated to disintegrate rapidly. Because of that formulation approach and the small size of the tablets, the tablets begin to disintegrate within seconds of contact with water (saliva). Therefore, bitterness may be perceived during the rapid disintegration of the tablet in the mouth prior to swallowing. Thicker coatings or alternative coating materials that dissolve more slowly in the mouth may delay the onset of perceived bitterness or eliminate it entirely if the delay is sufficient for the patient to swallow the tablet.

In the second route, bitterness may be perceived due to small amounts of dust from the API entrapped in the coating during the manufacturing process, as evidenced in some tablet samples subjected to scanning electron microscopy. A comparison of the current commercial tablets and a representative tablet with alternative coating shows clear differences in the gross physical appearance, as well as at a microscopic level (Figure 1). Reducing or eliminating API dust through a mechanical process (dedusting) prior to tablet coating may decrease perceived bitterness upon dose administration.

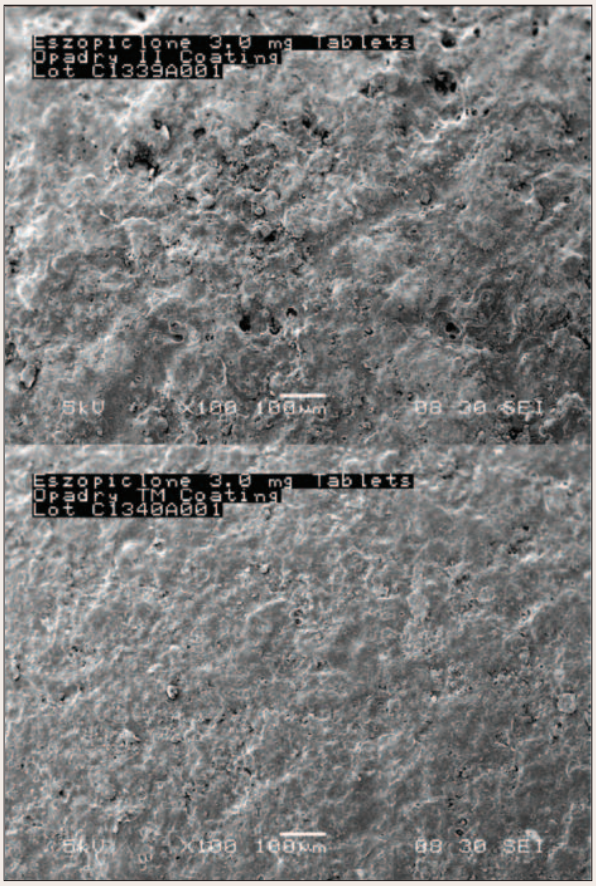
The objectives of this study were to evaluate the relationship between the film coating and the bitterness perceived during tablet administration and to determine how the coating or process variables affect time to bitter breakthrough.

## Materials and methods

**Study samples.** Six tablet coating variables that comprised different coating types, weights, and degree of tablet dedusting were evaluated, as shown in Figure 2. Coating materials supplied by Colorcon were applied to compressed tablet cores. The commercial process uses

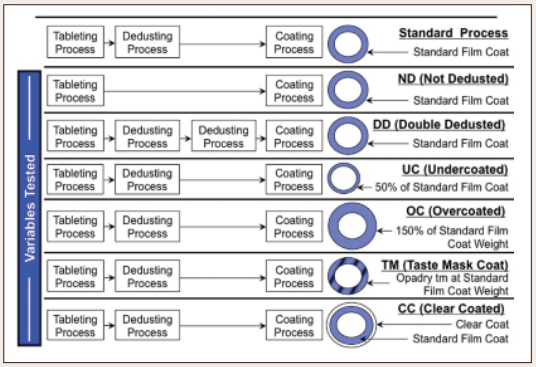
### Figure 1

**Micrographs of the coating used on the current commercial tablet (top) and the TM coating on a representative tablet**




### Figure 2

**Tablet coating variables comprised different coating types, weights, and degree of tablet dedusting.**



Opadry II coating (standard coating weight). The coatings tested were "undercoated" (UC) Opadry II (50 percent of standard coating), "overcoated" (OC) Opadry II (150 percent of standard coating), Opadry Taste Mask (TM) at the same standard coating weight, and standard weight Opadry II with an overcoat of Opadry Clear (CC) at 50 percent of the standard coating weight. Process variables of no dedusting (ND) and double-dedusting (DD) were created using a mechanical tablet deduster prior to a standard Opadry II coating. The tablets were manufactured by Patheon (Mississauga, ON, Canada).

**Taste evaluation.** The clinical study was an open-label study in healthy subjects who were trained sensory panelists. A clinical protocol and informed consent form were reviewed and approved by New England Institutional Review Board. As eszopiclone is a hypnotic agent, taste evaluations were conducted at panelists' homes in the evening and the number of sample evaluations per day was limited to ensure participant safety in the event of accidental swallowing. In addition, the panelists were instructed not to perform any activity that requires complete alertness, such as driving a car or operating machinery, for 8 hours following the assessment.

The panelists were trained in using the Flavor Profile method of descriptive sensory analysis in their evaluations and had 5 to 20 years of drug product evaluation experience. The onset of bitterness was evaluated using the seven-point category intensity scale of the Flavor Profile method (Table 1) [6]. Caffeine reference standards were used to establish the intensity values for the bitter basic tastes.

**TABLE 1**

**Flavor Profile scale**

| | Intensity |
|---|---|
| 0 | None |
| ½ | Very slight |
| 1 | Slight |
| 1 ½ | Slight to moderate |
| 2 | Moderate |
| 2 ½ | Moderate to strong |
| 3 | Strong |

The study was conducted in two parts. In Part 1, the panelists evaluated the tablets by licking the tablet surface (lick test) and in Part 2, the panelists evaluated the tablets by rolling them in the oral cavity (roll test), each of which is described below.

**Part 1: Lick test.** In the lick test, the tablet samples were evaluated following a fixed-sequence, repeated-measures design consisting of six evaluations of the tablet band followed by six evaluations of the tablet face. The two tablet surfaces were separately evaluated to explore potential differences in coating coverage based on tablet geometry. For each lick-test evaluation, the panelists held the tablet using polypropylene locking forceps–grasping by the band for evaluating the tablet face and by the face for evaluating the tablet band (Figure 3). The panelists repeatedly licked the test surface by drawing the tablet along the surface of the tongue from the center to the tip, applying slight and uniform pressure. After each lick, the panelists paused briefly to facilitate saliva distribution and perceive any bitterness. The panelists recorded the number of licks required to reach moderate-intensity bitterness on the Flavor Profile scale. The used tablets were placed into a receptacle for collection and destruction at the conclusion of the study.

**Part 2: Roll test.** In the roll test, panelists evaluated the bitterness of each tablet by gently rolling it in the oral cavity between the tongue and palate. Each sample type was evaluated three times. The order of sample presentation was randomized and samples coded (three-digit numeric) for blind evaluation by the panelists. As this was an open-label study, the panelists were aware that each sample contained API but were not aware of the coating variable. The panelists placed the tablet on the tongue and started a stopwatch. The panelists gently rolled the tablet between the tongue and palate and recorded the number of seconds required to reach a moderate intensity of bitterness using the Flavor Profile scale. The tablet was then expectorated into a receptacle for collection and destruction at the conclusion of the study.

**FIGURE 3**

**Orientation of forceps grasping the tablets in preparation for evaluation of the face and band of the tablets**

Band evalutation

Face evalutation

**Statistical analysis.** The lick-test and roll-test data were analyzed separately using a repeated-measures Analysis of Variance. The set of averages, computed for each panelist/coating variable/surface, was analyzed using an approach similar to one discussed by Winer [7]. A Bonferroni pairwise comparison test was used to determine significant differences between coating variables.

## Results

**Part 1: Lick test.** The mean lick-test results for the tablet bands along with upper and lower 95 percent confidence limits are shown in Figure 4. The mean number of licks to bitter breakthrough (bitter intensity ≥ 2 on the Flavor Profile scale) of the tablet bands ranged from 2.92 licks for Formulation UC to 8.38 licks for Formulation OC, with a 95 percent confidence interval of 1.63 licks.

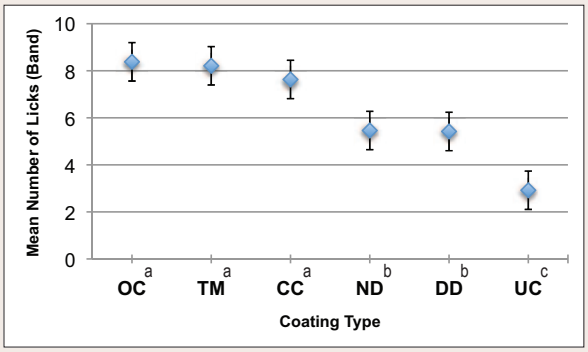
The corresponding lick-test results for the tablet faces are shown in Figure 5. The mean lick values on the face were similar to those of the band, with one transposition—Formulation TM required the most licks to bitter breakthrough. Variation was smaller on the tablet face evaluation, with a 95 percent confidence interval of 0.56 lick.

The lick-test data for the tablet band and face were highly correlated (Figure 6). The taste-mask, overcoat and clear-coat tablet variables (formulations TM, OC, and CC, respectively) required the most licks to reach bitter breakthrough as measured on either the band or face of the tablets. Tablet dedusting showed no effect on reducing bitter breakthrough as the double-dedusted and non-dedusted tablets (formulations DD and ND, respectively) were closely paired. The undercoated tablets (Formulation UC) required the fewest licks to reach bitter breakthrough, thereby showing a clear correlation between coating weight (or resultant thickness) and bitter breakthrough.

**Part 2: Roll test.** The mean roll times to bitter breakthrough with upper and lower 95 percent confidence limits are shown in Figure 7. The mean roll values ranged from 12.4 to 23.2 seconds, with undercoated tablets (UC) requiring the least time and overcoated tablets (OC) tablets requiring the most.

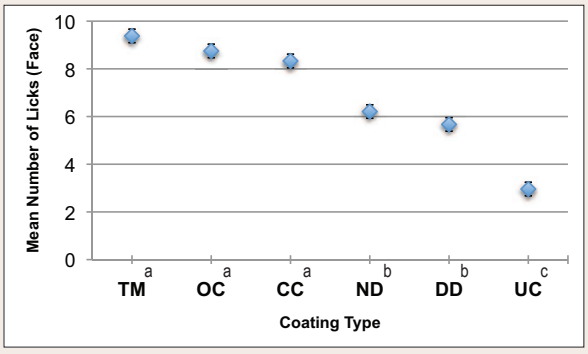
### Figure 4

**Mean number of licks until moderate-intensity bitter taste is perceived for the band of six coating types. Superscript letters are the results of Bonferroni's pairwise comparisons; means sharing the same letter are not statistically different ($p < 0.05$).**



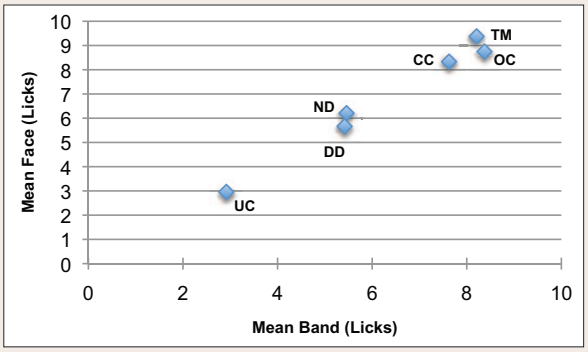

### Figure 5

**Mean number of licks until moderate-intensity bitter taste is perceived for the face of six coating types. Superscript letters are the results of Bonferroni's pairwise comparisons; means sharing the same letter are not statistically different ($p < 0.05$).**



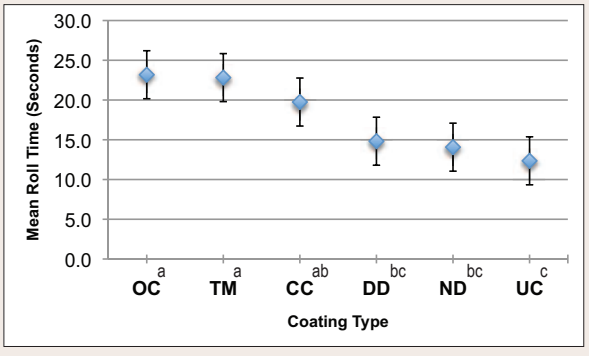

### Figure 6

**Correlation plot of face vs. band lick-test values**




### Figure 7

**Mean number of seconds until moderate-intensity bitter taste is perceived for six coating types. Superscript letters are the results of Bonferroni's pairwise comparisons; means sharing the same letter are not statistically different ($p < 0.05$).**



Fewer statistically different comparisons were detected amongst the coating variables using the roll-test data compared to the lick-test data; however the roll-test data are highly correlated with the lick-test data, as shown in Figure 8. This indicates that the lick test is a good predictor of bitter perception as would normally be perceived by a patient taking the tablet.

For the roll test, the six coatings fell into the same groupings observed for the lick test. The taste-mask, overcoat and clear-coat tablet variables (formulations TM, OC, and CC respectively) required the longest time to bitter breakthrough. Tablet dedusting showed no effect on reducing bitter breakthrough as the double-dedusted and non-dedusted tablets (formulations DD and ND, respectively) were closely paired. The undercoated tablets (Formulation UC) required the shortest time to bitter breakthrough.

## Discussion

Using a trained taste panel, alternative tablet coating formulations produced significant differences in bitter breakthrough. Specifically, tablets coated with Opadry Taste Mask and Opadry II with Opadry Clear were able to delay bitter onset when compared to Opadry II for all tests conducted. Increasing coating weight from 50 percent to 150 percent of the standard coating weight also delayed bitter breakthrough. Removal of API dust from the tablet cores however, did not alter bitter breakthrough.

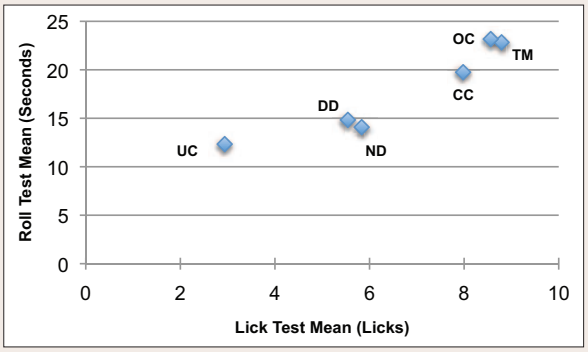
The results were similar and correlated between the three evaluation techniques used: (1) number of licks to bitter breakthrough of the tablet face; (2) number of licks to bitter breakthrough of the tablet band; and (3) number of seconds to bitter breakthrough rolling the tablet in the mouth.

Evaluating tablets by rolling them in the mouth succeeded in measuring differences between coating types, but it was the most variable method. This may be due to variations in panelist biology, such as oral cavity size and saliva flow rate. The lick method allows for the application of a uniform stroke length at a uniform pressure, which may account for the lower variability.

Among the lick methods, evaluation of the tablet face was less variable than the evaluation of the tablet band. This may be explained by more complete or uniform coating on the tablet face. The geometry of the tablet face has a wide convex surface area whereas the band has two edges that may be difficult to coat evenly, increasing variability. Alternatively, the larger surface contact area of the face may have improved repeatability by effectively aggregating coating thickness.

**FIGURE 8**

**Comparison of roll- and lick-test data**




## Conclusions

Applying experimental design of coating systems in combination with trained human taste panels can be used to develop tablet coatings that reduce bitterness perceived during dose administration. In this study, coating variables were found to have a greater effect on reducing time to bitter breakthrough than mechanical tablet dedusting. Sensory evaluation techniques whereby bitter breakthrough is measured by the number of licks of the tablet surface (lick test) or the time in the oral cavity (roll test) were both good predictors of bitter breakthrough. The lick test of the tablet face was the least variable of the techniques evaluated and has the additional benefit of reducing the likelihood that test subjects would inadvertently ingest tablets. *T&C*

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