Effect of Granule Size on Rough Mouth Feel and Palatability of Orally Disintegrating Tablets

S. Uchida, S-I. Kimura, H. Ogawa, N. Namiki
University of Shizuoka

Purpose
Orally disintegrating tablets (ODTs) are formulations that rapidly disintegrate in the oral cavity upon contact with saliva, and help improve compliance in patients who have difficulty ingesting prescribed medications. However, since ODTs are formulated to disintegrate in the oral cavity, they often lead to an unpleasant taste and a rough sensation on the tongue during administration, unlike conventional tablets. This unpleasant sensation can markedly affect medication compliance. Evaluation of formulation palatability is therefore essential for the development of ODTs. In general, tableting drugs with an unpleasant taste into ODTs commonly involves a physical masking procedure wherein drugs are coated with polymers to mask their unpleasant taste (taste-masked particles). However, these taste-masking particles are believed to contribute to the rough mouth feel of ODTs. Small particles sizes result in tablets that are less likely to feel rough to the tongue. However, the relationship between rough mouth feel and size of the taste-masked particles has not been elucidated thus far. In this study, we formulated ODTs containing core granules of different particle sizes, evaluated the palatability of these ODTs using a visual analog scale (VAS), and elucidated the effects of particle size of core granules on rough mouth feel and overall palatability of ODTs.

Methods
Core granules (microcrystalline cellulose spheres, Celphere®, type: CP-102, CP-203, CP-305, CP-507, Asahi Kasei Co. Ltd., Tokyo, Japan) were mixed with Ludiflash® (BASF Japan, Tokyo, Japan) and sodium stearyl fumarate, and ODTs having the following characteristics were prepared using a single-punch tablet machine: tablet diameter and weight: 9 mm and 300 mg per tablet, respectively, hardness: 50 N (measured values: 40-69 N), and disintegration time: <30 s (measured values: 15.1-22.7 s). To evaluate the mouth feel of granules of various sizes, 15 healthy volunteers (7 men and 8 women; mean age ± standard deviation [SD], 23.0 ± 2.6 years) were enrolled in a randomized crossover single-blind study. The subjects placed each ODT into their mouth for 60 s before spitting it out, and they were immediately asked to rate the rough mouth feel, need for water, and total palatability using VAS (100 mm representing the strongest sensation for each parameter). After the subjects rinsed their mouth cavities following the completion of the VAS evaluation, they were asked to evaluate the feeling of roughness and discomfort using a 5-point scale. All volunteers provided written consent for participation in the study. The study protocol was approved by the Ethics Committee at the University of Shizuoka.

Results
Evaluation of the relationship between particle size of core granules and rough mouth feel using ODTs containing core granules showed that large particle sizes intensified the rough mouth feel of the ODTs. Compared to the rough mouth feel VAS scores of the non-ODTs, which did not contain any core granules, the rough mouth feel VAS scores increased significantly immediately after the subjects spit out the ODTs containing core granules >c.a.200 μm (d10) in size, indicating intensification of the rough mouth feel. Similar to the VAS scores for rough mouth feel, VAS scores for the need for water increased for ODTs containing core granules of large particle sizes. In contrast, larger particle sizes of core granules corresponded to lower VAS overall palatability scores. Based on these data, receiver operating characteristic (ROC) analysis was performed to determine the threshold VAS scores for roughness and discomfort. Thus, rough mouth feel VAS scores of 33 and 52 were the threshold scores for roughness and discomfort, respectively. Based on the linear relationship between the rough mouth feel VAS scores and particle size, VAS scores of 33 and 52 were obtained for particle sizes of 244 μm (d10) and 453 μm (d10), respectively. Therefore, particle size (of the core granule contained within the ODT) of 244 μm was considered to be the particle roughness threshold. The subjects experienced discomfort at a particle size exceeding 453 μm, although the roughness was tolerable between these particle sizes.

Conclusion
Core granules with a particle size <200 μm, in particular, produced significantly intense rough mouth feel compared to non-ODTs. In addition, particle size (of the core granule contained within the ODT) of 244 μm was estimated to be the threshold for particle roughness. This study elucidated how the properties of masking particles influence rough mouth feel and palatability.