Assessment of Taste and Grittiness of Riomet® ER Strawberry, Riomet® ER Grape, Riomet® Cherry, and Metformin Immediate-Release Tablets in Healthy Subjects

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Abstract
Objective This study was conducted to evaluate the taste and grittiness of two formulations of Riomet® ER (metformin hydrochloride for extended release [ER] oral suspension 100 mg/mL) differing only in their flavoring agents (strawberry and grape) in comparison with two commercially available immediate-release (IR) formulations of metformin, Riomet® Cherry (metformin hydrochloride oral solution 500 mg/5 mL) and metformin IR tablets (metformin hydrochloride IR tablets 500 mg), in healthy human subjects aged 10–70 years.

Methods Five comparison sets (i.e., Riomet® Cherry vs. Riomet® ER Strawberry; Riomet® Cherry vs. Riomet® ER Grape; metformin IR vs. Riomet® ER Strawberry; metformin IR vs. Riomet® ER Grape; and Riomet® Cherry vs. metformin IR) were evaluated. Riomet® ER was reconstituted as instructed on the label. Metformin IR tablets were crushed one at a time into a fine powder using a pharmaceutical pill crusher and mixed with 5 mL of water. A 2.5-mL dose of each product was administered to each subject. Subjects were instructed not to swallow any of the products. Each product in the comparison set was rated by the subjects for taste and grittiness according to a 7-point hedonic facial scale and a 5-point level of agreement scale. A comparison questionnaire was also completed by the subjects after evaluating each set. In all, 56 subjects were enrolled and 55 subjects completed the study. The taste preference was statistically evaluated.

Results and Conclusions All Riomet® formulations were significantly preferred overall to metformin IR crushed tablets. Both the strawberry and the grape flavors of Riomet® ER tended to be preferred to Riomet® Cherry.

Key Points
Current metformin formulations are associated with compliance issues because of the bitter taste, the need for frequent dosage administrations and inconvenient dosing schedules, difficulties in swallowing due to large pill sizes, and dosing inflexibility because certain extended-release (ER) tablets cannot be broken.

In this study, the taste and grittiness of two formulations of Riomet® ER (metformin hydrochloride for ER oral suspension 100 mg/mL; flavored with strawberry and grape) were compared with two immediate-release (IR) formulations of metformin, Riomet® Cherry (metformin hydrochloride oral solution 500 mg/5 mL), and metformin IR tablets (metformin hydrochloride IR tablets 500 mg) in healthy human subjects.

All Riomet® formulations were significantly preferred to metformin IR crushed tablets. Both the strawberry and grape flavors of Riomet® ER tended to be preferred to Riomet® Cherry.
1 Introduction

Diabetes mellitus is a complex, chronic disease responsible for substantial morbidity and mortality in the USA and globally [1]. Type 2 diabetes mellitus (T2DM) requires continuous medical care for glycemic control and accounts for 90–95% of all diabetes [2]. Metformin hydrochloride (HCl) is a first-line oral antihyperglycemic drug used in the management of T2DM [3]. Metformin HCl improves glucose tolerance, lowers both basal and postprandial plasma glucose, decreases hepatic glucose production, decreases intestinal absorption of glucose, and helps to improve insulin sensitivity by increasing peripheral glucose uptake and utilization [4]. Metformin HCl is highly soluble in water and has an extremely bitter taste [5]. Since the taste of the oral dosage form is a critical parameter for ensuring patient compliance, it is necessary to mask the bitter taste of metformin HCl formulations to improve patient compliance [6].

Currently, metformin HCl is available for administration in immediate-release (IR) and extended-release (ER) dosage forms. Common problems associated with IR dosage forms include a bitter taste, the need for frequent dosage administration, and lack of compliance because of an inconvenient dosing schedule. The ER tablet dosage form is larger than the IR dosage form (due to a higher dose of metformin HCl) and must be taken whole [7], negating dose flexibility. In addition, ER tablets are large, which can make them hard to swallow, especially for geriatric populations who can have difficulty swallowing pills [8]. To overcome the problems associated with the currently available formulations, Sun Pharmaceuticals Industries, Inc. (Princeton, NJ, USA), has developed metformin HCl ER powder for oral suspension (PFOS; Riomet® ER) that offers reduced frequency of dose administration, ease of swallowability, dose flexibility, and an acceptable taste.

Metformin HCl PFOS comprises ER pellets and a vehicle for reconstitution. The ER pellet system (see Fig. 1) is prepared by layering the drug onto an insoluble core and covering the drug layer with an ER coating designed to meet the desired drug-release profile. The vehicle for reconstitution is designed such that upon reconstitution with ER pellets, the vehicle prevents leaching of the drug from the ER pellets into the vehicle throughout the reconstituted shelf life, but when ingested, the drug release starts. An IR component of the drug is also present in the vehicle for reconstitution to meet the desired drug-release profile. To minimize the gritty feeling associated with ER pellets in the mouth, the average ER pellet size was aimed at between 200 and 300 µm [9]. To mask the bitter taste of metformin HCl, flavoring agents and sweeteners were added to the drug layer. Furthermore, since the drug layer was coated with an ER layer, the bitter taste of metformin HCl was significantly masked by this design.

The objective of this consumer acceptability study was to evaluate the overall taste and grittiness of two formulations of metformin HCl PFOS suspension differing only in their flavoring agents (strawberry and grape) with two commercially available IR formulations, metformin HCl oral solution (OS; Riomet® Cherry; Sun Pharmaceutical Industries, Ltd.) and metformin HCl IR tablets (Zydus Pharmaceuticals, Pennington, NJ, USA), crushed and resuspended, in healthy subjects aged between 10 and 70 years.

2 Methods

2.1 Study Design

This was an open-label study to determine taste, grittiness, and overall acceptability of metformin HCl PFOS strawberry, metformin HCl PFOS grape, metformin HCl OS cherry, and metformin IR tablets in healthy male and female subjects. This study was conducted at TKL Research, Inc. (TKL; Fair Lawn, NJ, USA), and run in accordance with accepted standards for Good Clinical Practice and with TKL’s standard operating procedures. The population was divided into two cohorts: Cohort 1 consisted of 28 subjects between the ages of 10 and 17 years who completed the study, and cohort 2 consisted of 27 subjects between the ages of 18 and 70 years who completed the study.

The study protocol, informed consent form, and other information provided to subjects were approved by an institutional review board before study initiation. The study was conducted in accordance with accepted standards for Good Clinical Practice and the Declaration of Helsinki. Informed consent was obtained from all individual participants or their guardians/parents before participation in any study procedure or assessment.

All screening and product administration procedures were conducted over the course of three visits. Each

![Fig. 1 Metformin hydrochloride extended—release pellets](image-url)
subject who completed the study received a total of five comparison sets over three visits: two comparison sets at visits 1 and 2, and one comparison set at visit 3. The comparison sets evaluated at each visit are presented in Table 1.

Subjects were randomized according to a computer-generated randomization schedule, with all possible orderings of each product in each of the five comparison sets. Randomization schedules were assigned to consecutive subject numbers in random order. Two separate randomization schemes were prepared, one for each age cohort. Subjects were assigned to the next randomized sequence in chronological order of enrollment. The randomization schedule dictated which products the subject tasted at each visit.

2.2 Subject Selection

Healthy male and female volunteer subjects aged 10–70 years, of any race or ethnicity, and free of any systemic disorder, were included in the study. Each subject was informed about the nature of the study and provided written informed consent before participation in the study. Subjects were excluded if they had a history of, or were currently being treated for, diabetes (type 1 or type 2); had a known hypersensitivity to metformin, a history of hepatic insufficiency or alcoholism, or fructose intolerance; or were receiving systemic drugs, topical drugs, or medication (including some vitamins and/or other probiotic supplements) that, in the opinion of the investigator, could have interfered with the study results. Female subjects who were pregnant, planning a pregnancy during the study, or breastfeeding were excluded from the study. In addition, sexually active females of childbearing potential who were unwilling to use an acceptable form of contraception (such as, but not limited to, hormonal contraceptives, spermicide plus barrier, or intrauterine device) were excluded from the study. Subjects were also excluded on the taste-testing day if they had consumed any food or drink that may have affected their perception of taste (i.e., highly spiced meals or mint or mint-based products).

2.3 Study Procedure

This study was conducted across three visits (Table 1): visit 1 included subject screening. Subjects were administered the study products according to the administration methods presented in Table 2.

Figure 2 is a flow diagram of the tasting and grading procedure. At each visit, subjects cleansed their palates with water and a water biscuit before administration of the first study product. Each subject tasted 2.5 mL of the assigned study product according to the randomization schedule. The subjects tasted each product for approximately 10–15 s (no less than 5 s and no more than 15 s, measured on a timer), spit out the product, and immediately rinsed their mouths with water. Subjects were given a chilled Poland Spring water bottle (16.9 oz) to use for rinsing throughout the entire visit. Subjects then recorded their ratings of taste (“How would you rate the overall taste of this product?”) according to the 7-point hedonic facial scale (Fig. 2 [10], Supplemental Figure 1) and grittiness (“Did the product taste gritty [sandy]?”) according to a 5-point level of agreement scale for the question “did the product taste gritty (sandy)”. (1 = strongly disagree to 5 = strongly agree, Fig. 2 [11], Supplemental Figure 1). Between each product tasting, subjects ate a water biscuit and rinsed their mouths with water to cleanse their palates, and then had a 15-min rest period. After the second product tasting, subjects recorded their taste and grittiness ratings using the same scales as the first product tasting. Subjects also completed a comparison questionnaire to compare the overall taste, grittiness, and preference between study products in that comparison set. This process was repeated for each of the five comparison sets tested during the study. Subjects were required to remain at the test facility for 1 h after the last product tasting in the final comparison set of the visit. A registered nurse was present during each tasting for medical oversight.

2.4 Statistical Methods

TKL carried out all data management and statistical analyses. The source data consisted of the taste and grittiness ratings given to each of the products, the preferences for taste and grittiness, and an overall preference. The data were

| Visit number | Comparison sets evaluated |
|--------------|---------------------------|
| 1            | Set 1: metformin IR cherry OS vs metformin ER PFOS strawberry |
| 1            | Set 2: metformin IR cherry OS vs metformin ER PFOS grape |
| 2            | Set 3: metformin IR crushed tablet vs metformin ER PFOS strawberry |
| 2            | Set 4: metformin IR crushed tablet vs metformin ER PFOS grape |
| 3            | Set 5: metformin IR cherry OS vs metformin IR crushed tablet |

ER extended release, IR immediate release, OS oral solution, PFOS powder for oral solution

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Table 2  Study product administration

| Product                  | Physical form and dose | Administration                                                                 |
|--------------------------|------------------------|-------------------------------------------------------------------------------|
| Metformin HCl OS, cherry | Solution 500 mg/5 mL   | 2.5-mL dose per subject                                                       |
| Metformin HCl PFOS, strawberry | Suspension 100 mg/mL | Reconstituted per instructions on label; 2.5-mL dose per subject             |
| Metformin HCl PFOS, grape | Suspension 100 mg/mL  | Reconstituted per instructions on label; 2.5-mL dose per subject             |
| Metformin IR             | Tablet 500 mg          | Using a pharmaceutical pill crusher, one tablet per subject was crushed into a fine powder and mixed with 5 mL of water; 2.5-mL dose per subject |

*ER extended release, IR immediate release, OS oral solution, PFOS powder for oral solution*

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**Start of visit**

1. Eating a water biscuit and rinsing mouth with water
2. Administration of the first study product
3. Tasting product for approximately 10–15 seconds
4. Rinsing with water
5. Recording of taste and grittiness ratings according to the 7-point hedonic facial scale and the 5-point level of agreement scale, respectively
6. Eating a water biscuit and rinsing mouth with water, followed by a 15-minute break
7. Administration of the second study product
8. Repeat steps 3–6
9. Complete a comparison questionnaire to compare overall taste, grittiness, and preference between study products

**7-point hedonic facial scale**

- Super bad (1)
- Really bad (2)
- Bad (3)
- May be good/may be bad (4)
- Good (5)
- Really good (6)
- Super good (7)

**5-point level of agreement scale**

| Numeric score | Description          |
|---------------|----------------------|
| 1             | Strongly disagree    |
| 2             | Disagree             |
| 3             | Neither agree or disagree |
| 4             | Agree                |
| 5             | Strongly agree       |

**Fig. 2**  Flow diagram of tasting and grading procedure. 7-point hedonic facial scale: Reproduced from Thompson A, et al. © 2013, the author(s). 5-point level of agreement scale: Based on Vagias WM. © 2006, Clemson University

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exported to SAS® datasets for statistical analyses. The rating data were analyzed separately for each product pair for each rating/attribute utilizing Wilcoxon’s signed-rank test at a level of significance of \( p < 0.05 \); no adjustments were made for the number of tests performed. The preference data were analyzed for each product pair for each rating/attribute using binomial statistics. Analyses were conducted for each age cohort and for each comparison set.

### 3 Results and Discussion

#### 3.1 Subject Demographics and Disposition

A total of 56 subjects were enrolled in the study, and 55 subjects (98.2%) completed the study. One subject (1.8%) voluntarily withdrew from the study. Subject ages ranged from 10.0 to 69.0 years, with a mean age of 24.1 years. The study population was stratified by age: 10–17 (cohort 1) and 18–70 (cohort 2) years.

##### 3.1.1 Cohort 1 (Aged 10–17 Years)

A total of 28 subjects were enrolled and completed the study. Mean age (range) was 13.9 (10.0–17.0) years; 18 subjects (64.3%) were White/Caucasian and 10 (35.7%) were Black/African American. Subject ethnicity included non-Hispanic/Latino (19 subjects, 67.9%) and Hispanic/Latino (nine subjects, 32.1%). In total, 16 subjects (57.1%) were male and 12 (42.9%) were female.

##### 3.1.2 Cohort 2 (Aged 18–70 Years)

A total of 28 subjects were enrolled, and 27 subjects (96.4%) completed the study. One subject (3.6%) voluntarily withdrew from the study. Mean age (range) was 34.2 (18.0–69.0) years; 20 subjects (71.4%) were White/Caucasian and eight (28.6%) were Black/African American. Subject ethnicity included non-Hispanic/Latino (25 subjects, 89.3%) and Hispanic/Latino (three subjects, 10.7%). In total, 20 subjects (71.4%) were male and eight (28.6%) were female.

#### 3.2 Study Assessments

The overall preferences in each cohort and for the entire study population are provided in Table 3. Both cohorts had similar preferences for taste, grittiness and overall acceptability for each test product.

A descriptive summary of taste scores using the 7-point hedonic facial scale for all subjects is presented in Fig. 3. The descriptive summary of the grittiness score on the 5-point agreement scale for all subjects is shown in Fig. 4.

### 4 Discussion

Metformin HCl is first-line therapy for glycemic control in patients with T2DM [3] and is as efficacious as other oral antihyperglycemic drugs [4]. However, metformin HCl tablets are often associated with a metallic taste and ER tablets are large; both factors can lead to suboptimal adherence to therapy. Suboptimal adherence to treatment with oral antihyperglycemic medications, including metformin, is frequently reported [12, 13] and leads to decreased therapeutic efficacy (glycemic control), increased healthcare utilization, and reduced cost effectiveness [14–17]. Furthermore, while T2DM was a chronic disease once associated with older age, rates have increased in children and adolescents over recent decades [18]. Both populations report difficulty swallowing pills, which is a documented barrier to adherence, as is disliking taste or palatability [19–27].

In this open-label study, we report the acceptability of taste and level of grittiness of two flavors, strawberry and grape, of a PFOS formulation of ER metformin HCl (resuspended), cherry-flavored OS IR metformin HCl, and crushed metformin HCl tablets resuspended in water for two age cohorts, older children/adolescents and adults. As expected, in both age cohorts, all three liquid formulations were preferred by a higher proportion of subjects overall, for taste, and for level of grittiness compared with resuspended crushed tablets. Crushing or splitting tablets is often reported as mode by which patients try to overcome swallowing difficulties [25]. However, for many medications (including metformin ER tablets [7]), crushing or splitting tablets can change their qualitative or pharmacological properties, leading to documented pharmacological adverse consequences, and they are not approved to be modified in this way [7, 28–31].

Therefore, alternative formulations, both for IR and ER metformin, may improve patient compliance and provide safer and more palatable options for patients who do not like to take metformin tablets.

While older adults may have difficulty swallowing pills because of dysphagia [8], pediatric patients are often just not yet comfortable with swallowing pills. Among pediatric patients, acceptance of tablets increases with age [32]; however, a considerable percentage of adolescents still report some difficulties swallowing pills [33]. Different modes of behavioral training and aids can help individuals overcome their pill-swallowing difficulties [34, 35], but in the case of pediatric patients, many parents do not wish to participate in training programs [36]; for these patients, a liquid formulation may be more suitable.

Regulatory agencies have recognized the need for age-appropriate formulations of medications commonly prescribed to children [31, 37, 38]; these formulations should...
Table 3  Overall preference, taste preference, and grittiness preference by subjects in each cohort and the entire population

| Cohort | Comparison set 1 | Comparison set 2 | Comparison set 3 | Comparison set 4 | Comparison set 5 |
|--------|------------------|------------------|------------------|------------------|------------------|
|        | Met IR OS cherry | Met IR OS cherry | Met IR OS cherry | Met IR OS cherry | Met IR OS cherry |
|        | Met ER PFOS      | Met ER PFOS      | Met ER PFOS      | Met ER PFOS      | Met ER PFOS      |
|        | strawberry       | crushed tablet   | grape            | crushed tablet   | strawberry       |
|        | 32.1             | 67.9             | 32.1             | 67.9             | 0.0872           |
|        | 0.0872           | 0.0872           | 0.0872           | 0.0872           | < 0.0001         |
|        | 74.1             | 25.9             | 74.1             | 25.9             | 0.0192           |
|        | < 0.0001         | < 0.0001         | < 0.0001         | < 0.0001         | < 0.0001         |
|        | 0.1221           | 0.0522           | 0.1221           | 0.0522           | 0.0065           |
|        | < 0.0001         | < 0.0001         | < 0.0001         | < 0.0001         | < 0.0001         |
|        | 0.0065           | 0.0015           | 0.0065           | 0.0015           | < 0.0001         |
|        | < 0.0001         | < 0.0001         | < 0.0001         | < 0.0001         | < 0.0001         |

Percentage of subjects who preferred each product overall

| Cohort 1 | Cohort 2 | Total |
|----------|----------|-------|
| Percentage of subjects who preferred each product overall | | |
| Cohort 1 | 32.1 | 67.9 | 32.1 | 67.9 | 0 | 100 | 14.3 | 85.7 | 92.9 | 7.1 |
| p value<sup>a</sup> | 0.0872 | 0.0872 | 0.0872 | 0.0872 | < 0.0001 | < 0.0001 |
| Cohort 2 | 29.6 | 70.4 | 29.6 | 70.4 | 3.7 | 96.3 | 7.4 | 92.6 | 77.8 | 22.2 |
| p value<sup>a</sup> | 0.0522 | 0.0522 | 0.0522 | 0.0522 | < 0.0001 | < 0.0001 |
| Total | 30.9 | 69.1 | 30.9 | 69.1 | 1.8 | 98.2 | 10.9 | 89.1 | 85.5 | 14.5 |
| p value<sup>a</sup> | 0.0065 | 0.0065 | 0.0065 | 0.0065 | < 0.0001 | < 0.0001 |

Percentage of subjects who preferred the taste of each product

| Cohort 1 | Cohort 2 | Total |
|----------|----------|-------|
| Percentage of subjects who preferred the taste of each product | | |
| Cohort 1 | 28.6 | 71.4 | 25.9 | 74.1 | 0 | 100 | 10.7 | 89.3 | 92.9 | 7.1 |
| p value<sup>a</sup> | 0.0357 | 0.0192 | 0.0192 | 0.0192 | < 0.0001 | < 0.0001 |
| Cohort 2 | 33.3 | 66.7 | 29.6 | 70.4 | 3.7 | 96.3 | 7.4 | 92.6 | 81.5 | 18.5 |
| p value<sup>a</sup> | 0.1221 | 0.0522 | 0.0522 | 0.0522 | < 0.0001 | < 0.0001 |
| Total | 30.9 | 69.1 | 27.8 | 72.2 | 1.8 | 98.2 | 9.1 | 90.9 | 87.3 | 12.7 |
| p value<sup>a</sup> | 0.0065 | 0.0015 | 0.0015 | 0.0015 | < 0.0001 | < 0.0001 |

Percentage of subjects who preferred the level of grittiness of each product

| Cohort 1 | Cohort 2 | Total |
|----------|----------|-------|
| Percentage of subjects who preferred the level of grittiness of each product | | |
| Cohort 1 | 32.1 | 67.9 | 35.7 | 64.3 | 32.1 | 67.9 | 35.7 | 64.3 | 60.7 | 39.3 |
| p value<sup>a</sup> | 0.0872 | 0.1849 | 0.0872 | 0.1849 | 0.0872 | 0.1849 | 0.0872 | 0.1849 | 0.3449 |
| Cohort 2 | 74.1 | 25.9 | 55.6 | 44.4 | 40.7 | 59.3 | 51.9 | 48.1 | 77.8 | 22.2 |
| p value<sup>a</sup> | 0.0192 | > 0.5000 | 0.4421 | > 0.5000 | 0.4421 | > 0.5000 | 0.4421 | > 0.5000 | 0.0059 |
| Total | 52.7 | 47.3 | 45.5 | 54.5 | 36.4 | 63.6 | 43.6 | 56.4 | 69.1 | 30.9 |
| p value<sup>a</sup> | > 0.5000 | > 0.5000 | > 0.5000 | > 0.5000 | 0.0581 | 0.4188 | 0.0581 | 0.4188 | 0.0065 |

Cohort 1: aged 10–17 years, n = 28. Cohort 2: aged 18–70 years, n = 27. Total N = 55

ER extended release, IR immediate release, met metformin, OS oral solution, PFOS powder for oral solution

<sup>a</sup>Analysis compares the paired ratings (first rating) using Wilcoxon’s signed-rank test
Consumer Acceptability of Riomet® Oral Solution vs. Other Metformin Formulations

be palatable, easy to swallow, and safe. The development of age-appropriate formulations for use in pediatric patients can be challenging, as this is a heterogeneous population with regards to swallowing abilities, taste preferences, and dosage requirements [38, 39]. Grape, cherry, and red berry flavors are preferred in US and European pediatric markets; cherry and strawberry flavors are recommended for masking a bitter taste [31]. Thus, these flavors were used in our liquid formulations of metformin HCl. Here, both the strawberry-flavored and the grape-flavored PFOS ER metformin were preferred for taste by a significantly greater proportion of subjects aged 10–17 years compared with cherry-flavored OS IR metformin HCl. Adult subjects in this study also preferred the taste of the PFOS formulations over the cherry-flavored OS formulation, but the difference was not significant. Both age cohorts preferred the taste of both PFOS formulations and the OS formulations over the crushed metformin tablets to a significantly greater proportion. The results for the overall population regarding taste acceptability and preference were confirmed by the distribution of scores on the 7-point hedonic scale for each comparison set.

Along with taste, texture is an important aspect of palatability, a key component in designing pediatric formulations that will be acceptable to patients to ensure proper dosing and adherence [39, 40]. The PFOS formulations evaluated here contains pellets that are between 200 and 300 μm in diameter, which falls within the range for acceptable grittiness [9]. Among subjects aged 10–17 years, a numerically greater but nonsignificant proportion preferred the level of grittiness of the PFOS formulations over the OS formulation or the crushed tablets. This differs from the adult subjects, who preferred the OS formulation over the PFOS formulations; this was significant for the comparison between cherry OS and strawberry PFOS. For the overall population, there was no significant difference in the proportion of subjects who preferred the level of grittiness of the PFOS formulation compared with either the OS cherry or the crushed tablets; however, a significantly greater proportion of subjects overall preferred the level of grittiness of the OS cherry over the resuspended crushed tablets. Using a 5-point agreement scale, more subjects in the overall population agreed or strongly agreed that PFOS formulations were gritty compared with the OS cherry or even the crushed tablet.

There are limitations to this study. The first is that the mean age of adult subjects was 34.2 years; only two subjects were aged ≥ 60 years. Thus, we do not have an adequate representation of older adults to be able to extrapolate these data to that age group. Second, we used a 7-point hedonic
scale to record evaluation of taste. For pediatric patients, a 5-point hedonic facial scale is more frequently used and may be more appropriate for assessment of taste acceptability [41].

5 Conclusion

To improve adherence to treatment, new formulations of drugs for chronic diseases need to be developed for populations of patients who either have difficulty swallowing pills or find the palatability of their medication unacceptable. For metformin HCl, we have developed liquid formulations with flavors designed to mask the bad taste associated with metformin and to provide an alternative option for those patients who have difficulty swallowing pills. The two PFOS formulations provide an ER option, whereas the OS formulation provides an IR option, thus providing patients with a greater array of options to help them manage their T2DM.

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Compliance with Ethical Standards

Funding Sun Pharmaceuticals Industries, Inc.

Conflict of interest Allyson C. Marshall, Maureen Damstra and Michael Tuley are employees of TKL Research, Inc. Elena L. Schifando is an employee of Sun Pharmaceuticals Industries, Inc.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants or their guardians/parents included in the study.

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References

1. Demmer RT, Zuk AM, Rosenbaum M, Desvarieux M. Prevalence of diagnosed and undiagnosed type 2 diabetes mellitus among US adolescents: results from the continuous NHANES, 1999–2010. Am J Epidemiol. 2013;178(7):1106–13.

2. American Diabetes A. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes Care. 2018;41(Suppl 1):S13–27.

3. American Diabetes A. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2018. Diabetes Care. 2018;41(Suppl 1):S73–85.

4. Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, et al. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. JAMA. 2016;316(3):313–24.

5. Hermann LS, Melander A. Biguanides: basic aspects and clinical uses. In: Alberti KGMM, DeFronzo RA, editors. International textbook of diabetes mellitus, vol. 1. Chichester: Wiley; 1992. p. 773–95.

6. Milne CP, Bruss JB. The economics of pediatric formulation development for off-patent drugs. Clin Ther. 2008;30(11):2133–45.

7. GLUCOPHAGE® (metformin hydrochloride) tablets, for oral use. Full prescribing information. Princeton, NJ: Bristol-Myers Squibb Co. 2018. https://packageinserts.bms.com/pi/pi_glucophage.pdf. Accessed 17 Dec 2018.

8. Aslam M, Vaezi MF. Dysphagia in the elderly. Gastroenterol Hepatol (N Y). 2013;9(12):784–95.

9. Lopez FL, Bowles A, Gul MO, Clapham D, Ernest TB, Tuleu C. Effect of formulation variables on oral grittiness and preferences of multiparticulate formulations in adult volunteers. Eur J Pharm Sci. 2016;92:156–62.

10. Thompson A, Reader S, Field E, Shephard A. Open-label taste-testing study to evaluate the acceptability of both strawberry-flavored and orange-flavored amylmetacresol/2,4-dichlorobenzyl alcohol throat lozenges in healthy children. Drugs R D. 2013;13(2):101–7.

11. Vagias WM. Likert-type scale response anchors. Clemson International Institute for Tourism & Research Development, Department of Parks, Recreation and Tourism Management. Clemson University. 2006. http://media.clemson.edu/cbshs/prtm/research-resources-for-research-page-2/Vagias-Likert-Type-Scale-Response-Anchors.pdf. Accessed 17 Dec 2018.

12. Iglay K, Cartier SE, Rosen VM, Zarotsky V, Rajpathak SN, Radican L, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral anti-hyperglycemic agents in type 2 diabetes. Curr Med Res Opin. 2015;31(7):1283–96.

13. Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care. 2004;27(5):1218–24.

14. Nichols GA, Rosales AG, Kimes TM, Tunceli K, Kurytka K, Mavor P. The change in HbA1c associated with initial adherence and subsequent change in adherence among diabetes patients newly initiating metformin therapy. J Diabetes Res. 2016;2016:9687815.

15. Farmer AJ, Rodgers LR, Lonergan M, Shields B, Weedon MN, Donnelly L, et al. Adherence to oral glucose-lowering therapies and associations with 1-year HbA1c: a retrospective cohort analysis in a large primary care database. Diabetes Care. 2016;39(2):258–63.

16. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. Clin Ther. 2011;33(1):74–109.

17. Herman WH, Edelstein SL, Ratner RE, Montez MG, Ackermann RT, Orchard TJ, et al. Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. Am J Manag Care. 2013;19(3):194–202.

18. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. N Engl J Med. 2017;376(15):1419–29.

19. Hommel KA, Baldassano RN. Brief report: barriers to treatment adherence in pediatric inflammatory bowel disease. J Pediatr Psychol. 2010;35(9):1005–10.

20. Ingerski LM, Baldassano RN, Denson LA, Hommel KA. Barriers to oral medication adherence for adolescents with inflammatory bowel disease. J Pediatr Psychol. 2010;35(6):683–91.

21. Modi AC, Zeller MH, Xanthakos SA, Jenkins TM, Inge TH. Adherence to vitamin supplementation following adolescent bariatric surgery. Obesity (Silver Spring). 2013;21(3):E190–5.

22. Baguley D, Lim E, Bevan A, Pallet A, Faust SN. Prescribing for children—taste and palatability affect adherence to antibiotics: a review. Arch Dis Child. 2012;97(3):293–7.

23. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Patient-centred pharmaceutical design to improve acceptance of medications: similarities and differences in paediatric and geriatric populations. Drugs. 2014;74(16):1871–89.

24. Mennella JA, Roberts KM, Mathew PS, Reed DR. Children’s perceptions about medicines: individual differences and taste. BMC Pediatr. 2015;15:130.

25. Marquis J, Schneider MP, Payot V, Cordonier AC, Bugnon O, Hersberger KE, et al. Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. Int J Clin Pharm. 2013;35(6):1130–6.

26. Schiefe JT, Quinzer L, Klimm HD, Pruszyldo MG, Haeferli WE. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. Eur J Clin Pharmacol. 2013;69(4):937–48.

27. Fields J, Go JT, Schulze KS. Pill properties that cause dysphagia and treatment failure. Curr Ther Res Clin Exp. 2015;77:79–82.

28. Quijano Ruiz B, Desfontaine E, Arenas-Lopez S, Wang S. Pediatric formulation issues identified in paediatic investigation plans. Expert Rev Clin Pharmacol. 2014;7(1):25–30.

29. Bourdenet G, Giraud S, Artur M, Dutertre S, Dufour M, Lefebvre-Caussin M, et al. Impact of recommendations on changing medications in geriatrics: from prescription to administration. Fundam Clin Pharmacol. 2015;29(3):316–20.

30. Fodil M, Ngheim D, Colas M, Bourry S, Poisson-Salomon AS, Rezigue H, et al. Assessment of clinical practices for crushing medication in geriatric units. J Nutr Health Aging. 2017;21(8):904–8.

31. European Medical Agencies. Reflection paper: formulations of choice for the paediatric population. 2006. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf. Accessed 17 Dec 2018.

32. Ranmal SR, Cram A, Tuleu C. Age-appropriate and acceptable paediatric dosage forms: insights into end-user perceptions, preferences and practices from the Children’s Acceptability of Oral Formulations (CALF) Study. Int J Pharm. 2016;514(1):296–307.

33. Hansen DL, Tulinius D, Hansen EH. Adolescents’ struggles with swallowing tablets: barriers, strategies and learning. Pharm World Sci. 2008;30(1):65–9.

34. Forough AS, Lau ET, Steadman KJ, Cichero JA, Kyle GJ, Serrano WC500 00378 2.pdf. Accessed 17 Dec 2018.

35. IW, et al. Assessment of clinical practices for crushing medication in geriatric units: from prescription to administration. Fundam Clin Pharmacol. 2015;29(3):316–20.

36. Polaha J, Dalton WT 3rd, Lancaster BM. Parental report of medication acceptance among youth: implications for everyday practice. South Med J. 2008;101(11):1106–12.
37. European Medicines Agency. Guidelines on pharmaceutical development of medicines for paediatric use. 2013. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000045.jsp&mid=WC0b01ac0580925cc9. Accessed 17 Dec 2018.

38. Buckley LA, Salunke S, Thompson K, Baer G, Fegley D, Turner MA. Challenges and strategies to facilitate formulation development of pediatric drug products: safety qualification of excipients. Int J Pharm. 2018;536(2):563–9.

39. Zajicek A, Fossler MJ, Barrett JS, Worthington JH, Ternik R, Charkoftaki G, et al. A report from the pediatric formulations task force: perspectives on the state of child-friendly oral dosage forms. AAPS J. 2013;15(4):1072–81.

40. Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, Turner R, et al. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. Adv Drug Deliv Rev. 2014;73:14–33.

41. Mistry P, Batchelor H. Methodology used to assess acceptability of oral pediatric medicines: a systematic literature search and narrative review. Paediatr Drugs. 2017;19(3):223–33.