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ORIGINAL RESEARCH ARTICLE

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.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40268-018-0260-x) contains supplementary material, which is available to authorized users.

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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

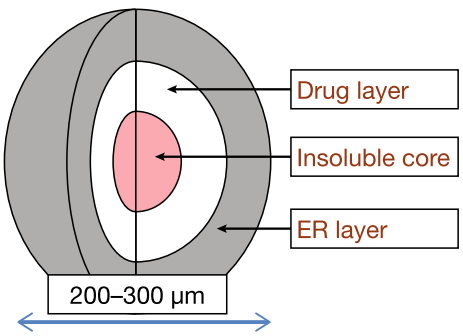

Fig. 1 Metformin hydrochloride extended—release pellets

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

Table 1 Visit number and comparison sets evaluated

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

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

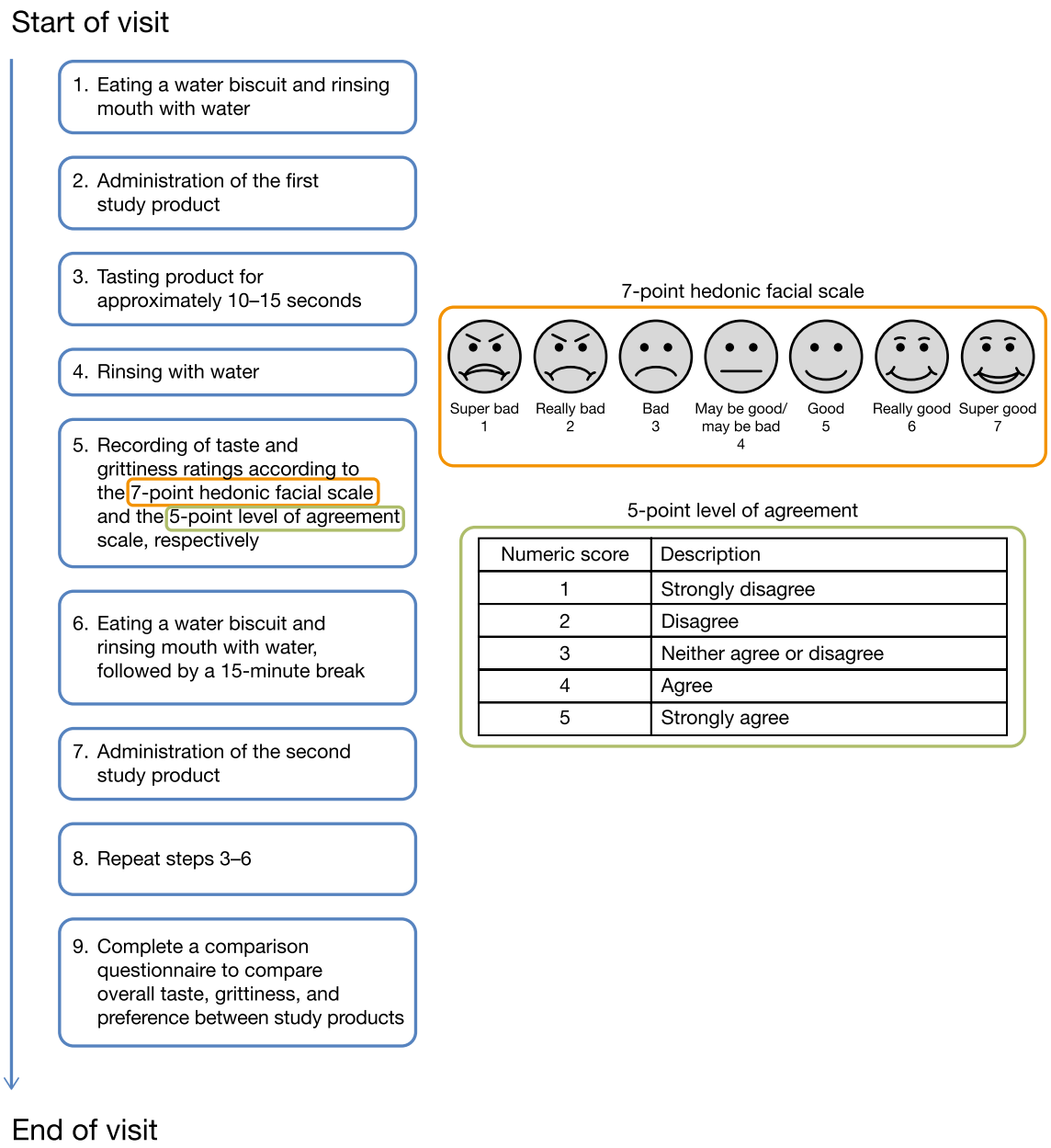

Fig. 2 Flow diagram of tasting and grading procedure. 7-point hedonic facial scale: Reproduced from Thompson A, et al. © 2013, the author(s). 5-point level of agreement scale: Based on Vagias WM.8 © 2006, Clemson University

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 acceptance 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 ER PFOS strawberry	Met IR OS cherry	Met ER PFOS grape	Met IR crushed tablet	Met ER PFOS strawberry	Met IR crushed tablet	Met ER PFOS grape	Met IR OS cherry	Met IR crushed tablet
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[a]	0.0872		0.0872		< 0.0001		0.0002		< 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[a]	0.0522		0.0522		< 0.0001		< 0.0001		0.0059	
Total	30.9	69.1	30.9	69.1	1.8	98.2	10.9	89.1	85.5	14.5
p value[a]	0.0065		0.0065		< 0.0001		< 0.0001		< 0.0001	
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[a]	0.0357		0.0192		< 0.0001		< 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[a]	0.1221		0.0522		< 0.0001		< 0.0001		0.0015	
Total	30.9	69.1	27.8	72.2	1.8	98.2	9.1	90.9	87.3	12.7
p value[a]	0.0065		0.0015		< 0.0001		< 0.0001		< 0.0001	
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[a]	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[a]	0.0192		> 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[a]	> 0.5000		> 0.5000		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

[a]Analysis compares the paired ratings (first rating) using Wilcoxon's signed-rank test

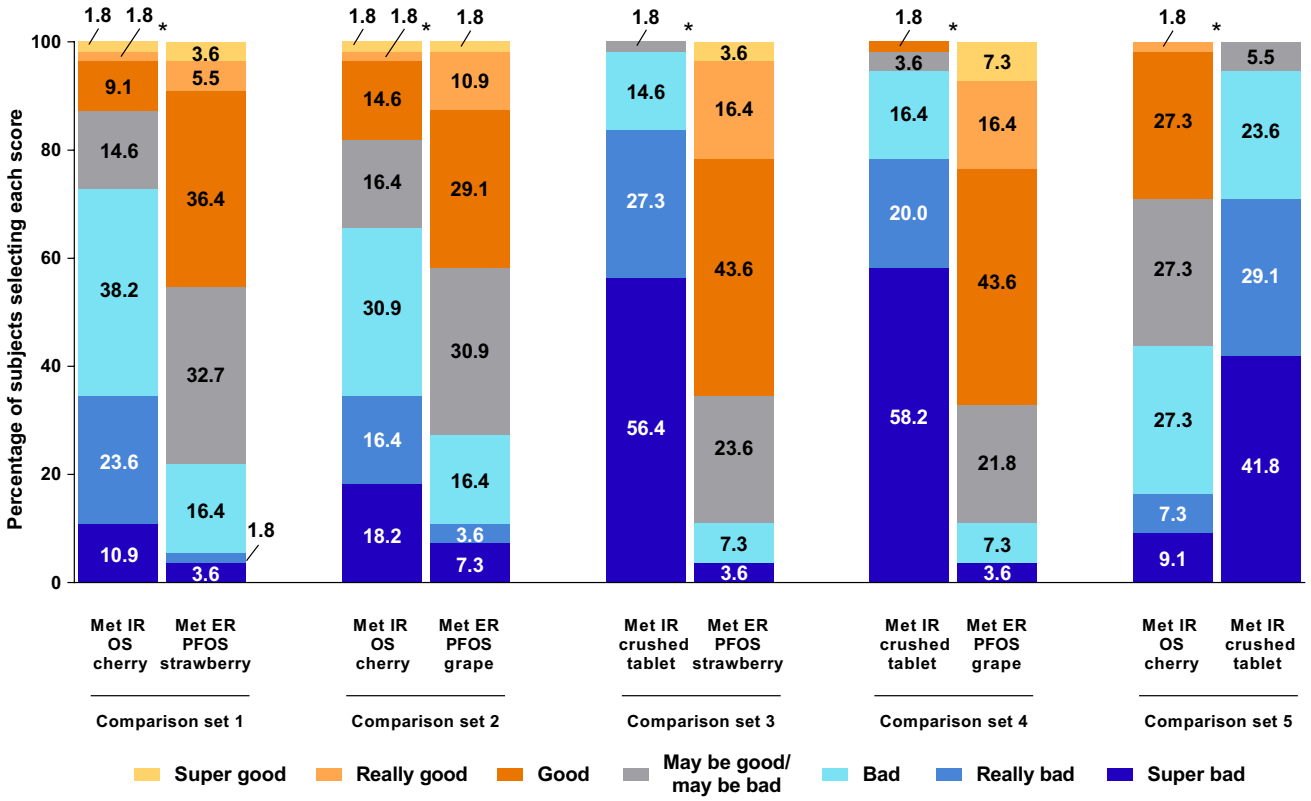

Fig. 3 Summary of taste score on 7-point hedonic facial scale for all subjects. * $p \leq 0.0001$; analysis compares the paired ratings (first rating) using Wilcoxon's signed-rank test. *ER* extended release, *IR* immediate release, *met* metformin, *OS* oral solution, *PFOS* powder for oral solution

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

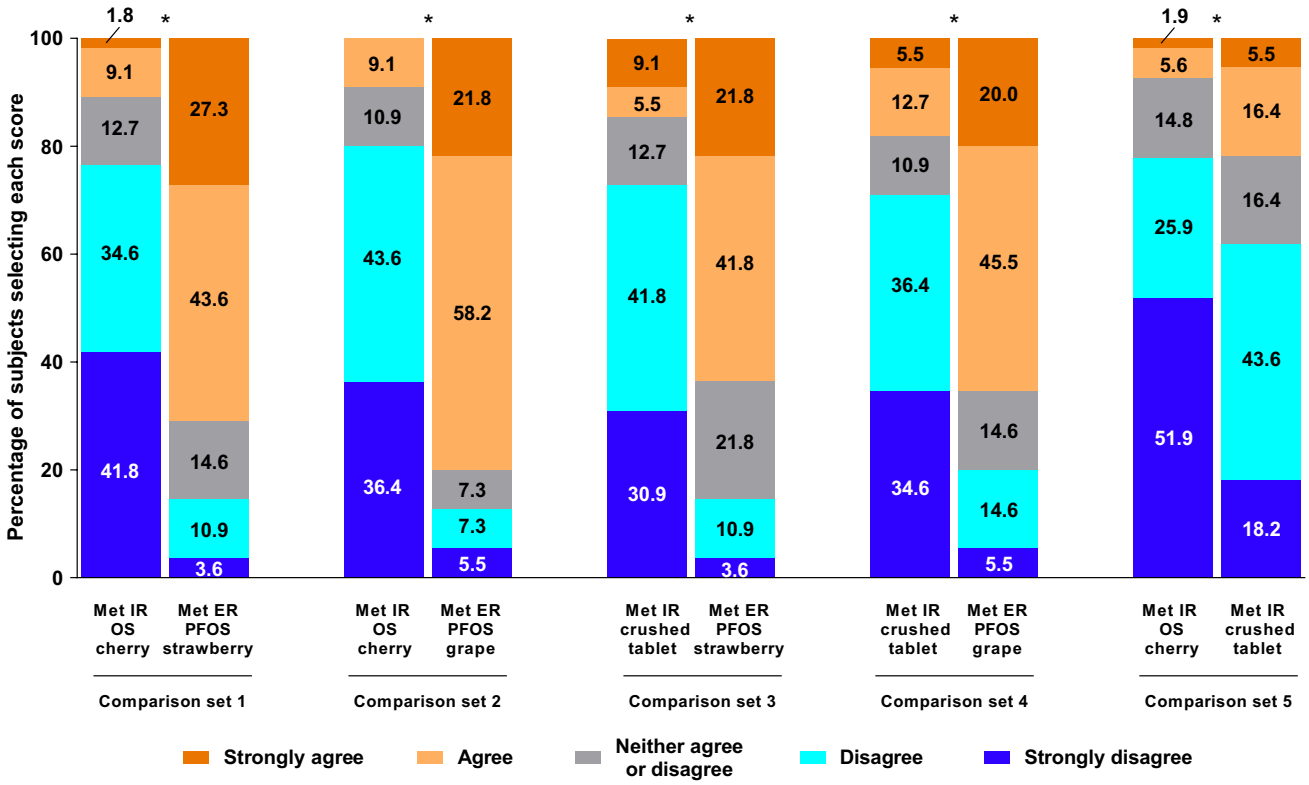

Fig. 4 Summary of grittiness score on 5-point agreement scale for the question "did the product taste gritty (sandy)", (1 = strongly disagree to 5 = strongly agree) for all subjects. *p value ≤ 0.0001; analysis compares the paired ratings (first rating) using Wilcoxon's signed-rank test. *ER* extended release, *IR* immediate release, *met* metformin, *OS* oral solution, *PFOS* powder for oral solution

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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