

A study to evaluate taste, grittiness, and overall acceptability of metformin extended-release powder for oral solution strawberry, metformin ER PFOS grape, metformin oral solution cherry, and metformin immediate-release tablets in healthy subjects

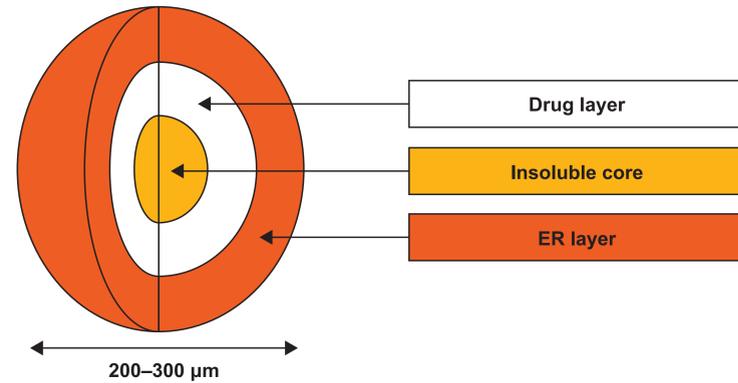
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INTRODUCTION

- Metformin hydrochloride (HCl) is a first-line oral antihyperglycemic drug used in the management of type 2 diabetes¹
- There is a need for metformin oral solutions for children, elderly, and patients with dysphagia
- While metformin HCl immediate-release (IR) is highly soluble in water, it has an extremely bitter taste, and taste masking is a challenge to improve compliance²
- Metformin HCl extended-release (ER) tablets are large and not crushable, and are difficult to swallow for some patients
- Sun Pharmaceutical Industries, Ltd., has developed a metformin HCl ER powder for oral solution (PFOS) that offers reduced frequency of dose administration, ease of swallowing, dose flexibility, and an acceptable taste
 - The ER pellet system (**Figure 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

Figure 1. Metformin HCl ER pellets



ER, extended release; HCl, hydrochloride.

OBJECTIVE

- The objective of this consumer acceptability study was to evaluate the overall taste and grittiness of 2 formulations of metformin HCl ER PFOS differing only in their flavoring agents (strawberry and grape) with 2 commercially available IR formulations of metformin, cherry-flavored metformin HCl IR oral solution (Riomet[®] Cherry; Sun Pharmaceutical Industries, Ltd.) and resuspended crushed metformin IR tablets (Zydus Pharmaceuticals, Pennington, NJ), in healthy subjects between 10 and 70 years of age

METHODS

- This open-label study enrolled healthy male and female subjects, aged 10 to 70 years, into 2 age cohorts: 10 to 17 years of age (Cohort 1) and 18 to 70 years of age (Cohort 2)
- Subjects with a known sensitivity to metformin or who had a fructose intolerance were excluded, as were subjects taking any kind of medication that might interfere with study results as well as females of childbearing potential not willing to use acceptable contraception
- Within each cohort, subjects were randomized to different schedules of comparison sets (**Table 1**)

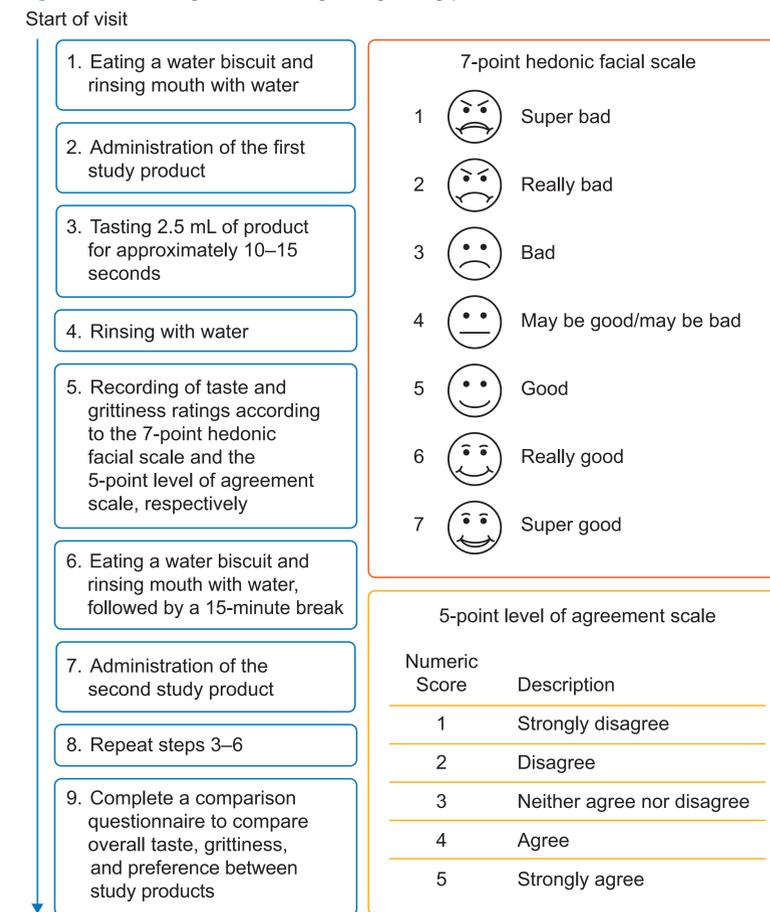
Table 1. Visit number and comparison sets evaluated

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

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

- Metformin ER PFOS strawberry and grape were provided in a 100-mg/mL suspension; metformin IR cherry oral solution (OS) as 500-mg/5-mL solution, and metformin IR 500-mg tablets were crushed into a fine powder and mixed with 5 mL of water
 - All study products were administered in 2.5-mL doses
- The procedure for the assessment of preference, taste, and grittiness for each study product are shown in **Figure 2**

Figure 2. Flow diagram of tasting and grading procedure^{3,4}



End of visit

- Statistical analyses were conducted for each comparison set within each cohort and for the overall population at a significance level of $p < 0.05$; no adjustments were made for the number of tests performed
- Adverse events (AEs) were recorded throughout the study

RESULTS

Subjects

- Of the 56 subjects enrolled, 55 (98.2%) completed the study; 1 subject in cohort 2 voluntarily withdrew
- In cohort 1 (ages 10–17 years), mean (standard deviation [SD]) age was 13.9 (1.9) years; 16 (57.1%) subjects were male, 18 (64.3%) were White/Caucasian, and 10 (35.7%) were Black/African American
- In cohort 2 (ages 18–70 years), mean (SD) age was 34.2 (16.8) years; 8 (28.6%) subjects were male, 20 (71.4%) were White/Caucasian, and 8 (28.6%) were Black/African American

Study product assessments

Table 2. Overall preference, taste preference, and grittiness preference by subjects in each cohort and the entire population

Cohort	Percentage of subjects who preferred each product overall									
	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
Cohort 1 (n = 28)	32.1	67.9	32.1	67.9	0	100	14.3	85.7	92.9	7.1
<i>p value</i> ^a	0.0872		0.0872		<0.0001		0.0002		<0.0001	
Cohort 2 (n = 27)	29.6	70.4	29.6	70.4	3.7	96.3	7.4	92.6	77.8	22.2
<i>p value</i> ^a	0.0522		0.0522		<0.0001		<0.0001		0.0059	
Total (N = 55)	30.9	69.1	30.9	69.1	1.8	98.2	10.9	89.1	85.5	14.5
<i>p value</i> ^a	0.0065		0.0065		<0.0001		<0.0001		<0.0001	

Cohort	Percentage of subjects who preferred the taste of each product									
	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
Cohort 1 (n = 28)	28.6	71.4	25.9	74.1	0	100.0	10.7	89.3	92.9	7.1
<i>p value</i> ^a	0.0357		0.0192		<0.0001		<0.0001		<0.0001	
Cohort 2 (n = 27)	33.3	66.7	29.6	70.4	3.7	96.3	7.4	92.6	81.5	18.5
<i>p value</i> ^a	0.1221		0.0522		<0.0001		<0.0001		0.0015	
Total (N = 55)	30.9	69.1	27.8	72.2	1.8	98.2	9.1	90.9	87.3	12.7
<i>p value</i> ^a	0.0065		0.0015		<0.0001		<0.0001		<0.0001	

Cohort	Percentage of subjects who preferred the level of grittiness of each product									
	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
Cohort 1 (n = 28)	32.1	67.9	35.7	64.3	32.1	67.9	35.7	64.3	60.7	39.3
<i>p value</i> ^a	0.0872		0.1849		0.0872		0.1849		0.3449	
Cohort 2 (n = 27)	74.1	25.9	55.6	44.4	40.7	59.3	51.9	48.1	77.8	22.2
<i>p value</i> ^a	0.0192		>0.5000		0.4421		>0.5000		0.0059	
Total (N = 55)	52.7	47.3	45.5	54.5	36.4	63.6	43.6	56.4	69.1	30.9
<i>p value</i> ^a	>0.5000		>0.5000		0.0581		0.4188		0.0065	

^aAnalysis compares the paired ratings (first rating) using Wilcoxon's signed-rank test. IR, immediate release; met, metformin; OS, oral solution; PFOS, powder for oral solution; ER, extended-release.

- In both age cohorts and overall, metformin ER PFOS strawberry and grape were significantly preferred to crushed metformin IR tablets and metformin OS cherry
- Additionally, subjects in both cohorts significantly preferred metformin OS cherry to crushed metformin tablets
- Both cohorts had similar preferences for taste, grittiness, and overall acceptance for each test product

Table 3. Descriptive summary of taste score on 7-point hedonic facial scale for all subjects

Taste score	Percentage of subjects selecting each score (N = 55)									
	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
1: Super bad	10.91	3.64	18.18	7.27	56.36	3.64	58.18	3.64	9.09	41.82
2: Really bad	23.64	1.82	16.36	3.64	27.27	0	20.00	0	7.27	29.09
3: Bad	38.18	16.36	30.91	16.36	14.55	7.27	16.36	7.27	27.27	23.64
4: May be good/may be bad	14.55	32.73	16.36	30.91	1.82	23.64	3.64	21.82	27.27	5.45
5: Good	9.09	36.36	14.55	29.09	0	43.64	1.82	43.64	27.27	0
6: Really good	1.82	5.45	1.82	10.91	0	18.18	0	16.36	1.82	0
7: Super good	1.82	3.64	1.82	1.82	0	3.64	0	7.27	0	0
<i>p value</i> ^a	<0.0001		0.0001		<0.0001		<0.0001		<0.0001	

^aAnalysis compares the paired ratings (first rating) using Wilcoxon's signed-rank test. IR, immediate-release; met, metformin; OS, oral solution; PFOS, powder for oral solution; ER, extended-release.

- A significantly greater proportion of subjects gave higher taste scores to the metformin ER PFOS strawberry and grape formulations vs metformin IR OS cherry or dissolved crushed metformin IR tablets

Table 4. Descriptive summary of grittiness score on 5-point agreement scale for all subjects

Grittiness score	Percentage of subjects selecting each score (N = 55)									
	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
Strongly disagree	41.82	3.64	36.36	5.45	30.91	3.64	34.55	5.45	51.85	18.18
Disagree	34.55	10.91	43.64	7.27	41.82	10.91	36.36	14.55	25.93	43.64
Neither agree nor disagree	12.73	14.55	10.91	7.27	12.73	21.82	10.91	14.55	14.81	16.36
Agree	9.09	43.64	9.09	58.18	5.45	41.82	12.73	45.45	5.56	16.36
Strongly agree	1.82	27.27	0	21.82	9.09	21.82	5.45	20.00	1.85	5.45
<i>p value</i> ^a	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	

^aAnalysis compares the paired ratings (first rating) using Wilcoxon's signed-rank test. IR, immediate-release; met, metformin; OS, oral solution; PFOS, powder for oral solution; ER, extended-release.

- A significantly greater proportion of subjects gave higher grittiness scores (meaning less gritty) to the metformin ER PFOS strawberry and grape formulations vs metformin IR OS cherry or dissolved crushed metformin IR tablets

Safety

- Three AEs were reported by 3 subjects during the study; 2 events of vomiting and 1 of toothache
 - All 3 were mild, resolved, and not considered related to study products

CONCLUSIONS

- Metformin ER PFOS strawberry and grape formulations appear to be more palatable than metformin IR OS cherry and dissolved crushed metformin IR tablets
- This new formulation may provide a new option for the management of type 2 diabetes mellitus in patients who are unable or unwilling to swallow tablets

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