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Effect of Food and Alternative Dosing Methods on the Pharmacokinetics of KP415, an Investigational ADHD Product Containing the Prodrug, Serdexmethylphenidate (SDX)

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BACKGROUND

- KP415 is an investigational ADHD product containing serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), co-formulated with d-MPH HCl in a fixed dose ratio of 70% SDX CI:30% d-MPH HCl
- KP415 has been designed as a once-daily, oral product whereby early exposure
 is governed by the 30% molar load of d-MPH HCl and mid- to late-day exposure is
 governed primarily by the 70% molar load of SDX, which is gradually converted to
 d-MPH throughout the day
- Because the onset and duration of d-MPH exposure it a critical determinant of ADHD symptom control over the course the day, it is important to examine external factors such as food that may impact these parameters
- Further, because some patients have difficulty swallowing intact capsules, it is important to ascertain whether alternative dosing methods, such stirring the capsule contents in liquid or sprinkling the contents on food, alter the PK profile

OBJECTIVE

 To assess the effects of food and alternative dosing methods (capsule contents sprinkled on applesauce or stirred in water) on the pharmacokinetics (PK) of single doses of KP415 capsules

METHODS

Subjects and Study Design

- This was an open-label, single dose, four-treatment, four-period, randomized crossover study of the effect of food and alternative dosing methods (stirred in water or sprinkled on applesauce) on the pharmacokinetics of KP415 capsules after oral administration in healthy volunteers under fed and fasted conditions
- Eligible subjects were healthy males and non-pregnant, non-breastfeeding females 18-55 years of age
- Eligible subjects were randomized to receive single doses of KP415 capsule (56 mg SDX Cl/12 mg d-MPH HCl; molar equivalent to 40 mg d-MPH HCl), separated by a washout period of at least 96 hours, under the following conditions:
- Treatment A: intact capsule under fasted conditions
- Treatment B: contents of one capsule stirred in water under fasted conditions
- Treatment C: contents of one capsule sprinkled on applesauce under fasted conditions
- Treatment D: intact capsule under fed conditions (FDA standard high-fat, high-calorie breakfast)
- Blood samples for PK analyses were collected pre-dose and at 0.5, 1, 2, 3, 4.5, 6, 7, 7.5, 8, 8.5, 9, 10, 12, 13, 24, 36, 48, 60, and 72 hours post-dose
- Adverse events were continuously recorded, and safety assessments were conducted throughout the study

Statistical Analyses

• The following plasma PK parameters for d-MPH were calculated: maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), apparent terminal half-life ($T_{1/2}$), area under the concentration-time curve (AUC_{0-24}), AUC_{0-last} , AUC_{0-linf} , and partial AUCs

- A statistical comparison of the d-MPH PK parameters of exposure (C_{max}, AUC_{0-last}, AUC_{0-last}, AUC_{0-inf}, AUC₀₋₂₄, and other partial AUCs) among the 4 treatments was performed using an Analysis of Variance (ANOVA) model on the In-transformed data for a 4-way crossover design with sequence, period and treatment as the fixed effects and subject within sequence as a random effect
- The least squares geometric means (LSGM) of the PK parameters for each treatment are reported, as well as point estimates and 90% Confidence Intervals (CI) for the Test to Reference ratios of geometric means

RESULTS

Subject Disposition and Demographics

- Of 30 subjects who enrolled in the study, 28 were included in the PK Population
- The overall population was comprised of 43.3% males, had a mean age of 36.4 years, and a mean weight of 78.0 kg

Pharmacokinetic Data

- Figure 1 shows mean concentration-time profiles for d-MPH across fasted (intact capsule, stirred in water, sprinkled on applesauce) and fed conditions
- Following administration of KP415 capsule, mean d-MPH plasma concentration-time profiles exhibited a single peak occurring at approximately 2.00 hours after dosing under fasted and fasted/stirred in water conditions (Treatments A and B) and at approximately 4.50 h after dosing under fasted/sprinkled on applesauce and fed conditions (Treatments C and D), followed by a decline through 36 hours postdose
- Mean d-MPH concentrations were slightly higher after fasted/sprinkled on applesauce and fed conditions (Treatments C and D) than after fasted and fasted/stirred in water conditions (Treatments A and B)
- Table 1 provides derived PK parameters for the 4 conditions tested

Figure 1. Mean plasma d-MPH concentration-time profiles following KP415 administration

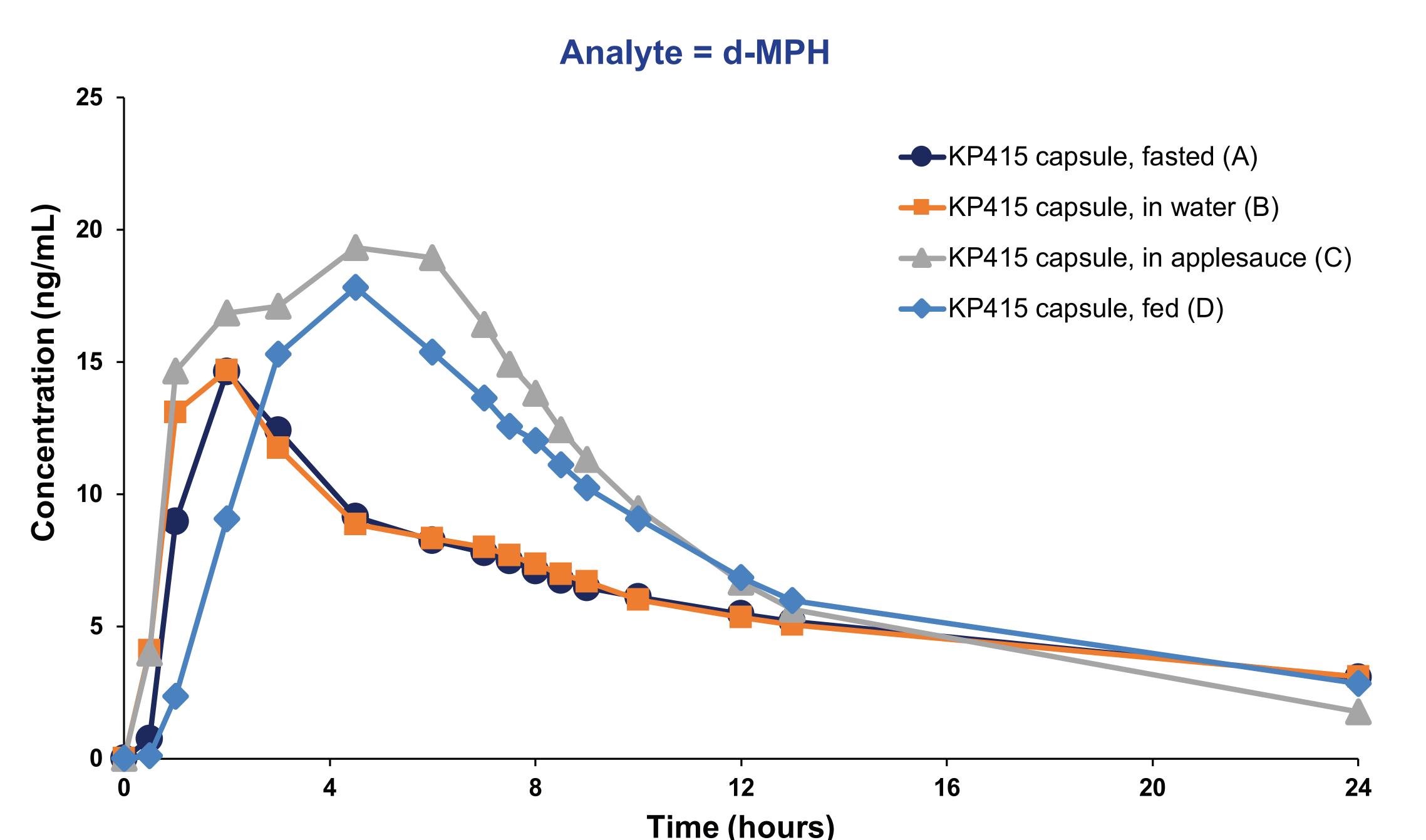


Table 1. Plasma PK parameters of d-MPH following administration of KP415 capsules

	KP415 Capsule Administration				
	Fasted	Stirred in water	Sprinkled in applesauce	Fed	
Parameter, Mean (SD)	Treatment A	Treatment B	Treatment C	Treatment D	
C _{max} (ng/mL)	15.2 (5.3)	15.9 (6.1)	20.9 (9.2)	18.5 (4.9)	
AUC _{0-24 hr} (h*ng/mL)	147.7 (49.3)	152.3 (48.4)	213.0 (83.7)	186.8 (63.6)	
AUC _{0-last} (h*ng/mL)	196.7 (74.9)	199.9 (66.9)	230.5 (87.7)	225.1 (84.0)	
AUC _{0-inf} (h*ng/mL)	202.3 (75.7)	207.3 (64.2)	234.9 (87.3)	229.8 (84.3)	
T _{max} (h)*	2.0 (1-8)	2.0 (1-3)	4.5 (1-7)	4.5 (3-7)	
T _{1/2} (h)	9.6 (2.2)	10.1 (2.7)	7.2 (2.0)	8.2 (1.3)	

*Values for T_{max} are median (range).

- Table 2 shows statistical analyses of d-MPH exposure under the 4 treatment conditions
- When KP415 capsule contents were stirred in water under fasted conditions, peak (C_{max}) and overall (AUC_{0-24hr}, AUC_{0-last}, and AUC_{0-inf}) d-MPH exposure were similar to that from intact KP415 capsules under fasted conditions (**Table 2A**)
- When KP415 capsule contents were sprinkled on applesauce under fasted conditions or administered under fed conditions, peak exposure was 24% and 34% higher, respectively, relative to KP415 capsules under fasted conditions (**Table 2B** and **2C**)
- Similarly, overall exposure, as expressed by AUC_{0-24hr}, was 42% and 27% higher, respectively, relative to fasted conditions, although there were little differences in AUC_{0-last} and AUC_{0-inf}
- Mean d-MPH T_{1/2} were similar across treatments, ranging from 7.15 h to 10.11 h

Table 2. Statistical analysis of the natural log-transformed systemic exposure of d-MPH comparing single oral dose administrations of KP415 capsules

A) Fasted, capsule contents stirred in water (Test) vs. Fasted, Intact Capsule (Reference)

Dependent	Geometric Mean		Ratio (%)	90% CI	
Variable	Test	Ref	(Test/Ref)	Lower	Upper
In(C _{max})	14.81	14.40	102.89	95.92	110.36
In(AUC _{0-24hr})	144.23	140.01	103.01	98.35	107.89
In(AUC _{0-last})	188.59	184.15	102.41	98.35	106.64
In(AUC _{0-inf})	197.96	190.26	104.05	99.96	108.29
In(AUC _{0-3hr})	30.15	25.68	117.42	101.52	135.80
In(AUC _{3-7hr})	34.84	34.95	99.70	94.07	105.66
In(AUC _{7-12hr})	30.31	30.18	100.43	94.21	107.06

B) Fasted, sprinkled on applesauce (Test) vs. Fasted, Intact Capsule (Reference)

Dependent	<u>Geometric Mean</u>		Ratio (%)	90% CI	
Variable	Test	Ref	(Test/Ref)	Lower	Upper
In(C _{max})	19.23	14.40	133.59	124.55	143.28
In(AUC _{0-24hr})	199.27	140.01	142.33	135.89	149.07
In(AUC _{0-last})	216.15	184.15	117.38	112.73	122.22
In(AUC _{0-inf})	221.14	190.26	116.23	111.67	120.97
In(AUC _{0-3hr})	34.83	25.68	135.67	117.31	156.90
In(AUC _{3-7hr})	67.18	34.95	192.24	181.39	203.73
In(AUC _{7-12hr})	50.81	30.18	168.38	157.96	179.48

C) Fed, Intact Capsule (Test) vs. Fasted, Intact Capsule (Reference)

Dependent	Geometric Mean		Ratio (%)	o (%) 90% C	
Variable	Test	Ref	(Test/Ref)	Lower	Upper
In(C _{max})	17.79	14.40	123.56	115.19	132.53
In(AUC _{0-24hr})	177.20	140.01	126.56	120.83	132.56
In(AUC _{0-last})	212.31	184.15	115.29	110.72	120.05
In(AUC _{0-inf})	217.26	190.26	114.19	109.71	118.86
In(AUC _{0-3hr})	15.27	25.68	59.47	51.42	68.78
In(AUC _{3-7hr})	61.17	34.95	175.03	165.14	185.50
In(AUC _{7-12hr})	46.19	30.18	153.07	143.60	163.18

Adverse Events

- Across all treatments, a total of 38 AEs was reported by 15 subjects (50%)
- Overall, the most common AEs were agitation (3 subjects, 10%), increased energy (4 subjects, 13.3%), and dry mouth (3 subjects, 10%)
- There were no serious AEs or AEs that led to a subject discontinuation

CONCLUSIONS

- In general, food did not impede drug absorption and production of KP415-derived d-MPH, and it appears that KP415 capsules may be administered without regard to food.
- The capsule contents stirred in water or sprinkled on applesauce are acceptable alternative modes of KP415 administration based on similar d-MPH exposure when compared to administration of the intact capsule.

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