

In Vitro Dissolution and *In Vivo* Oral Absorption of Methylphenidate from a Bimodal Release Formulation in Healthy Volunteers

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ABSTRACT:

Purpose—The objective of this study was to evaluate the *in vitro* dissolution and *in vivo* absorption of D,L-threo-methylphenidate (MPH) from a novel bimodal release formulation (Ritalin[®] LA capsule) compared with an immediate-release formulation (Ritalin IR tablet) in healthy volunteers.

Methods—The bimodal release formulation contains 50% of the dose in the immediate-release (IR) beads and 50% in polymethacrylate-coated, delayed-release (DR) beads. To better understand the impact of dissolution from the DR beads on oral absorption of MPH, three Ritalin LA formulations with different dissolution profiles for the DR beads (referred to as slow-, medium and fast-release formulations) were prepared, and tested together with the immediate-release formulation in 18 healthy male and female volunteers after a single oral dose under fasted conditions. The rate and extent of oral absorption of MPH were evaluated based on the overall C_{\max} , t_{\max} and AUC values, as well as the C_{\max} , t_{\max} and AUC values for each individual peak of the bimodal plasma concentration-time profile. The *in vivo* absorption-time profile was also examined by deconvolution.

Results—All three Ritalin LA formulations demonstrated similar bimodal plasma concentration-time profiles with two peak concentrations observed at ~2 and ~6 h post dose, mimicking that of Ritalin IR tablets given 4 h apart. Deconvolution results showed that the absorption of MPH was biphasic, with a rapid absorption phase between 0 to ~2 h, and a somewhat slower second absorption between ~3–6 h, consistent with the *in vitro* bimodal release characteristics of Ritalin LA formulation. The three Ritalin LA formulations were bioequivalent to one another based on the overall C_{\max} and AUC values and the corresponding values describing the first and second peaks, although their *in vitro* dissolution profiles for the DR beads were different. Compared with Ritalin IR, the Ritalin LA formulation demonstrated a similar rate of absorption for the first peak, a lower second C_{\max} and a higher trough concentration between peaks, as well as similar overall plasma AUC .

Conclusions—Following a single oral drug administration, Ritalin LA demonstrated a two-peak plasma concentration-time profile, similar to that of the IR formulation given 4 h apart, but with

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less fluctuation in the plasma concentration–time profile. The *in vivo* biphasic absorption of MPH appeared to be well correlated with the bimodal dissolution characteristics of this new Ritalin LA formulation, and some changes in the dissolution profiles for the DR beads appeared not to affect the overall bioavailability of MPH in humans. Copyright © 2004 John Wiley & Sons, Ltd.

Key words: Ritalin; methylphenidate; dissolution; absorption; human

Introduction

Methylphenidate (a racemic mixture of D-,L-enantiomers, MPH, Ritalin[®]), a well-established psychostimulant, has been the drug of choice for the treatment of children with attention-deficit hyperactivity disorder (ADHD) [1]. Although the mechanism of action of methylphenidate in ADHD is not well established, it may be attributable in part to the inhibition of dopamine reuptake. MPH blocks the transporter for dopamine and, to some extent, noradrenaline (norepinephrine), resulting in the inhibition of reuptake of these monoamines into the presynaptic neuron. Because of the short half-life of 2 to 3 h, MPH is often administered two or three times a day to maintain therapeutic concentrations throughout the normal school day [2–4]. While modified-release formulations of MPH were developed to alleviate the need for multiple daily dosing, the onset of action of these formulations is perceived to be slow, and they do not appear to be as clinically effective as the immediate-release formulations given twice per day [5,6]. The onset of clinical effects with MPH appears to be related to the rate of change in MPH plasma concentrations [6–7], and a continuous release of drug from a sustained-release formulation may result in tachyphylaxis [9].

Ritalin LA is a new long-acting bimodal release formulation of MPH, formulated using the technology known as the spheroidal oral drug absorption system (SODASTM) [10,11]. In this formulation, MPH is film-coated onto sugar spheres to produce IR beads, and a portion of these IR beads are then coated with a polymer to form DR beads that effect the required second delayed release. The polymer used for the DR beads controls the rate of water entering and solubilizing the drug, and controls the rate at which the solubilized drug diffuses out of the microparticulate pellet for absorption. *In vivo*

studies in humans have shown that this new Ritalin LA formulation produced double-peak concentration–time profiles of MPH, mimicking that of Ritalin tablet, an immediate release formulation given 4 h apart [11]. In children with ADHD it has been demonstrated that a 20 mg oral dose of Ritalin LA can significantly improve the behavioural and cognitive responses compared with placebo [11]. At the same dose level, the peak concentration and *AUC* values in adults [11,12,13] were approximately half of those in children [11] suggesting that the pharmacokinetics of Ritalin LA in children are similar to that in adults after correction for the body size differences. A high fat breakfast or apple sauce had no effect on the initial rate and overall plasma concentrations of MPH, and no dose dumping was observed [13].

In the present study, the *in vivo* absorption and bioavailability of Ritalin LA with different release properties were studied and compared with the immediate-release formulation, Ritalin[®] IR tablet in healthy adult volunteers. The *in vitro* dissolution was performed at two pH conditions, acidic and neutral pH, and the *in vivo* bioavailability was evaluated based on the overall C_{\max} , t_{\max} and *AUC* values, as well as the C_{\max} , t_{\max} and *AUC* values for each individual peak of the bimodal plasma concentration–time profile. The *in vivo* absorption characteristics of MPH were examined by deconvolution.

Materials and Methods

Drug product

Methylphenidate in its immediate-release formulation (Ritalin IR tablet) and its bimodal release formulation (Ritalin LA capsule) were from Novartis Pharmaceuticals Corporation, East Hanover, NJ. The Ritalin LA modified-release

capsules were produced using a dual bead fill system, comprising IR beads and DR beads. The IR beads were prepared by dissolving the drug substance and polyethylene glycol in purified water. This solution was coated onto sugar spheres and subsequently, half the IR beads were coated with a combination of ammonio methacrylate copolymer and methacrylic acid copolymers to obtain the DR beads. Varying amounts of coating suspension were used for each formulation in order to obtain the desired release profile; i.e. slow-, medium- and fast-release formulations, respectively.

In vitro

The *in vitro* dissolution testing was performed in a USP apparatus (basket) at a rotation speed of 100 rpm. The *in vitro* dissolution of the three Ritalin LA formulations was first determined in an acidic medium (0.01 N HCl) for 2 h, then the remaining beads were transferred into a neutral pH medium (phosphate buffer pH 6.8) and dissolution was monitored at 4, 6, 8 and 10 h. Baskets were used in the transfer of beads from the acidic medium to the neutral pH medium. The *in vitro* dissolution of Ritalin IR tablets was tested only in the low pH medium.

In vivo

This was a four-treatment, four-period, single-dose, randomized crossover design study involving 17 healthy volunteers (8 male, 9 female, mean age 32 ± 8.79 years). The mean (\pm SD) height and weight were 168 (\pm 11.24) cm and 71.7 (\pm 16.34) kg, respectively. All subjects received all four treatments, three Ritalin LA capsule formulations (40 mg) and Ritalin IR tablets (two 20 mg given 4 h apart) as the reference, with a 4- to 7-day washout period between each treatment period.

The number of subjects included in the study was determined based on the intra-patient CV estimated (16% and 18% for dose-normalized AUC_{0-t} and $C_{max(abs)}$, respectively) based on previous data (Novartis internal information). Assuming this CV for the Ritalin LA formulations, a sample size of 16 subjects would have at least 80% probability for the 90% confidence interval (CI) to fall within the bioequivalence

range of 80%–125% if the mean difference was less than 7% for AUC_{0-t} (5% for $C_{max(abs)}$) for the slow- or fast-release compared with the medium-release.

Drug administration and blood sampling

Study medication was administered with 200 ml of water after at least a 10 h fast. Subjects were instructed not to chew the medication, but to swallow it whole. Unless performing a study assessment, subjects rested quietly in the upright position for the next 4 h and did not assume the recumbent position during this time. The second Ritalin IR tablet was administered with 200 ml of water 4 h later, and regular lunch was provided at the same time, 4 h after the morning dose.

All blood samples (5 ml) were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein at predose and 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16 and 24 h post-morning doses for both Ritalin LA and IR tablets. For the Ritalin IR tablet, the 4 h blood sample was taken at the same time as the second tablet was administered. Blood samples were centrifuged for plasma and kept frozen at or below -20°C pending analysis.

Sample analysis

Plasma samples were assayed using a high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) that was developed and validated for the quantification of racemic methylphenidate in human plasma. Methylphenidate and its internal standard were extracted from plasma by liquid–liquid extraction (LLE) [14]. The method is suitable for the routine analysis of racemic methylphenidate in human plasma with a validated limit of quantitation of 0.05 ng/ml using a sample volume of 400 μl . Calibration was performed within the range 0.05–100 ng/ml and correlation coefficients were ≥ 0.998 . The mean accuracy of calibrator (standard) samples for 0.05–100 ng/ml were 96.5%–103%, and CVs 1.50–9.52%. The intra- and inter-day accuracy and precision values for the QC samples at the lower limit of quantification (LLOQ) or above are summarized below.

At LLOQ, intra-day accuracy was within the range 82.6%–100% and intra-day precision was

within the range 5.29%–9.08%. Above LLOQ, the intra-day accuracy was within the range 88.9%–105% and the intra-day precision was within the range 0.797%–5.00%. At LLOQ, the inter-day accuracy was 93.2% and the inter-day precision was 10.6%. Above LLOQ, the inter-day accuracy was within the range 95.5%–102% and inter-day precision was within the range 3.79%–7.46%. Stability studies at room temperature are reported in the previous enantiomeric methods [15].

Pharmacokinetic data analysis

Plasma concentrations of MPH were reported at the actual time points for each subject by treatment period. All subjects who completed at least one treatment period and had a complete pharmacokinetic profile were included in the pharmacokinetic data analysis. Values below the limit of quantitation were set to 0 for pharmacokinetic analysis and missing values were labelled accordingly and were not included in the analysis. For each treatment period, the pharmacokinetic profiles were analysed by standard non-compartmental methods using WinNonlin™ (version 1.5, Pharsight, Palo Alto, CA).

The maximum (peak) plasma MPH concentration ($C_{\max(\text{abs})}$) and the time to reach the peak concentration ($t_{\max(\text{abs})}$) were recorded as observed from time 0 to the last measurable concentration (C_t) time point. The area under the concentration–time curve (AUC) from time 0 to the last measurable concentration time point (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$) were calculated by a linear trapezoidal method, with the extrapolated $AUC_{t-\infty}$ calculated as C_t divided by the terminal elimination rate constant (k_e). $C_{\max(\text{abs})}$, $t_{\max(\text{abs})}$, AUC_{0-t} and $AUC_{0-\infty}$ were considered as primary pharmacokinetic parameters for bioavailability comparison for the different MPH formulations. The peak concentration, time to peak concentration, and AUC values for the first peak from time 0 to 4 h and the second peak from 4 to 8 h of the bimodal concentration–time profile were considered as secondary pharmacokinetic parameters. In addition, the elimination half-time associated with the terminal slope (k_e) of a semilogarithmic concentration–time curve was determined as $0.693/k_e$.

The fraction absorbed for MPH was calculated by using the Wagner–Nelson deconvolution method assuming the pharmacokinetics of MPH follows a one-compartment model after an oral drug administration

$$f_t = \frac{C_t + k_e AUC_{0-t}}{k_e AUC_{0-\infty}} \quad (1)$$

where f_t is the fraction absorbed until time t , and $C(t)$ is the plasma concentration as a function of time (t). The fraction of MPH absorbed was determined for each individual and each of the Ritalin LA treatments by using the above method. Subsequently, the mean fraction absorbed was calculated for each of the Ritalin LA treatments.

Statistical data analysis

The relative bioavailability of the formulations was compared in the context of an analysis of variance (ANOVA) model for a 4×4 crossover design. The pair-wise comparisons of AUC or C_{\max} values between the Ritalin LA formulations were made using the medium-release formulation as the reference and the contrast within the ANOVA. A pair-wise comparison between the slow- and fast-release Ritalin LA formulations was also performed. A conventional 90% CI was constructed for the difference in the least square means between two formulations. The antilogs of the confidence limits so obtained constitute the 90% CI for the ratio of the geometric means on the original scale. For the times to reach the peaks in the plasma concentration–time profiles, $t_{\max(0-4)}$, $t_{\max(4-8)}$ and $t_{\max(\text{abs})}$, statistical analysis was conducted based on the signed rank test. The nonparametric 90% and 95% CI for the median difference were computed for the within-subject differences between treatments [16].

Results and Discussion

A total of 17 subjects entered the study; 16 subjects completed all treatments of the study. One subject dropped out of the study after the first treatment period (Ritalin LA medium release) for an unknown reason not related to any adverse event during treatment. The

administered dose, 40 mg, was generally well tolerated and no difference in any adverse events such as sleepiness or dry mouth was observed between Ritalin LA and IR tablets given b.i.d. All adverse events are categorized as mild in severity for all formulations tested.

The plasma concentration–time profiles, pharmacokinetic and statistical comparison results for MPH are shown in Figure 1 and Tables 1, 2a and 2b. The *in vitro* dissolution and *in vivo* absorption (fraction absorbed) time profiles are shown in Figures 2 and 3.

Following single dose administration of 40 mg Ritalin LA capsules, the three Ritalin LA formulations with three different *in vitro* release

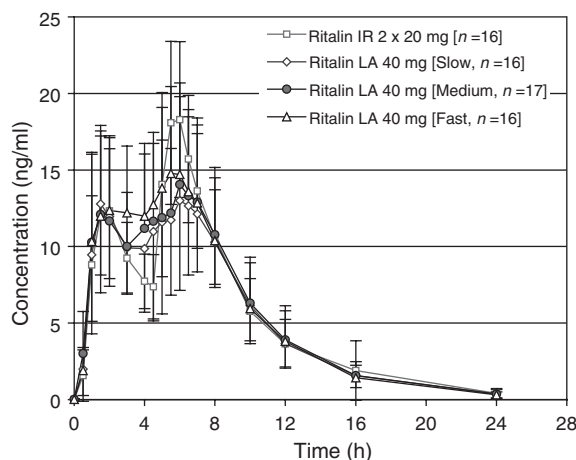


Figure 1. Plasma concentration (mean \pm SD)-time profile of MPH after a single dose of Ritalin LA slow-, medium- or fast-release formulation and Ritalin tablets (immediate release formulation) given 4 h apart

profiles all produced bimodal plasma concentration–time profiles with the 1st and 2nd peaks being observed at \sim 2 and \sim 6 h, respectively, mimicking the plasma concentration–time profiles of Ritalin IR tablets given 4 h apart. The two-peak plasma concentration–time profiles are very similar to that reported previously conducted under similar experimental conditions in adults [11–13] and in children [11]. The C_{\max} and AUC values in the present study (40 mg) are also similar to those reported previously at a lower dose 20 mg [11] after correction for the dose differences. These plasma concentration–time profiles correlated well with the bimodal dissolution profiles as observed *in vitro*, but this correlation appeared to be not significant among the three Ritalin LA formulations with different DR beads.

The three Ritalin LA formulations all consist of the same amount of drug in the immediate release beads and delayed release beads, 50% of the dose each. As expected, all three formulations showed similar initial rates and extent of dissolution within the first 2 h in a low pH medium (0.01 N HCl) (Figure 2). These results confirmed the release of the active ingredient from the IR beads and the integrity of the polymethacrylate coating on the DR beads; the latter did not dissolve or release MPH at low pH conditions regardless of the amount of polymer being coated. After transferring the beads remaining in the dissolution baskets to the neutral medium, the dissolution of methylphenidate from the three Ritalin LA formulations appeared to be similar except for the time of delay (or lag

Table 1. Pharmacokinetic parameters of MPH following a single dose of Ritalin LA 40 mg (slow-, medium- or fast-release formulation) and two 20 mg doses of Ritalin-IR given 4 h apart

Parameter	Arithmetic mean \pm SD			
	Ritalin LA, slow $n = 16$	Ritalin LA, Medium $n = 17$	Ritalin LA, fast $n = 16$	Ritalin-IR $n = 16$
AUC_{0-t} (ng.h/ml)	127.1 \pm 36.9	132.4 \pm 47.7	135.7 \pm 46.5	133.9 \pm 41.3
$AUC_{0-\infty}$ (ng.h/ml)	129.2 \pm 38.1	134.3 \pm 48.8	137.3 \pm 47.1	136.0 \pm 42.6
$C_{\max(0-4)}$ (ng/ml)	13.5 \pm 4.5	14.0 \pm 5.5	14.1 \pm 5.0	13.2 \pm 4.9
$t_{\max(0-4)}$ (h)	1.8 \pm 0.7	2.2 \pm 1.1	2.5 \pm 1.1	1.7 \pm 0.5
$C_{\max(4-8)}$ (ng/ml)	15.5 \pm 5.1 ^a	17.0 \pm 6.4 ^a	17.0 \pm 5.5 ^a	19.5 \pm 5.3
$t_{\max(4-8)}$ (h)	6.2 \pm 1.0	5.8 \pm 1.0	5.5 \pm 1.0	5.7 \pm 0.26
$t_{1/2}$ (h)	3.5 \pm 0.66	3.3 \pm 0.54	3.2 \pm 0.48	3.3 \pm 0.6
F_{rel} (%)	97.3 \pm 14.1	97.0 \pm 12.6	101.2 \pm 13.8	100

^aNot different among one another, but all significantly different from Ritalin-IR.

Table 2a. Statistical evaluation of slow- or fast-release Ritalin LA formulations with medium-release Ritalin LA formulation), and slow-release Ritalin LA formulation with fast-release Ritalin LA formulation, following oral administration of a single 40 mg dose in healthy subjects

Parameter	Slow vs medium ^a		Fast vs medium		Slow vs fast		Medium vs IR tablet	
	LS mean ratio	90% CI for ratio	LS mean ratio	90% CI for ratio	LS mean ratio	90% CI for ratio	LS mean ratio	90% CI for ratio
AUC_{0-t} (ng.h/ml)	1.00	(0.95, 1.05)	1.04	(0.99, 1.10)	0.96	(0.91, 1.01)	0.96	(0.91, 1.02)
$AUC_{0-\infty}$ (ng.h/ml)	1.00	(0.95, 1.05)	1.04	(0.99, 1.10)	0.96	(0.91, 1.01)	0.96	(0.91, 1.02)
$C_{max(0-4)}$ (ng/ml)	1.02	(0.89, 1.16)	1.04	(0.92, 1.19)	0.97	(0.85, 1.11)	1.03	(0.90, 1.18)
$C_{max(4-8)}$ (ng/ml)	0.95	(0.87, 1.03)	1.04	(0.96, 1.13)	0.91	(0.84, 0.99)	0.82	(0.75, 0.90)

^aSlow and fast are the test treatments and medium is the reference treatment. *P* value, LS Mean ratio, and 90% confidence interval for true mean ratio are determined from an ANOVA model with sequence, subject (sequence), period, and treatment as factors, with subject (sequence) as random effect.

Table 2b. Statistical evaluation of slow- or fast-release Ritalin LA formulations with medium-release Ritalin LA formulation following single oral administration of a 40 mg dose in healthy subjects

Parameter	Slow vs medium		Fast vs medium		Slow vs fast		Medium vs IR tablet	
	Median difference ^a	<i>p</i> -value	Median difference	<i>p</i> -value	Median difference	<i>p</i> -value	Median difference	<i>p</i> -value
$t_{max(0-4)}$ (h)	0.0	0.717	0.3	0.246	-0.8	0.080	0.0	0.566
$t_{max(4-8)}$ (h)	0.0	0.346	-0.5	0.127	0.8	0.028	0.5	0.349

^aMedian Difference is the median of the pairwise differences of slow and fast release formulations. *p*-value is for median difference, determined nonparametrically by Wilcoxon's signed rank test.

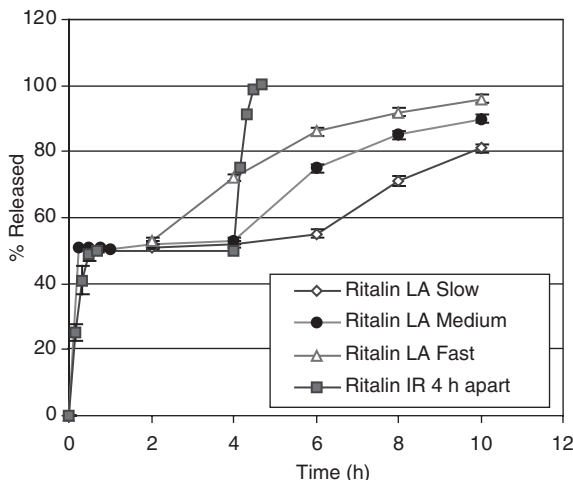


Figure 2. *In vitro* dissolution profiles of three Ritalin LA formulations, slow, medium and fast, and Ritalin IR tablet. For Ritalin LA, the dissolution medium was changed at 2 h from acidic pH medium (0.01 N HCl) to neutral pH medium (pH 6.8). For comparison purposes, the dissolution profile for Ritalin-IR tablet at 4 h was simulated assuming the dissolution of the second dose was the same as the first dose

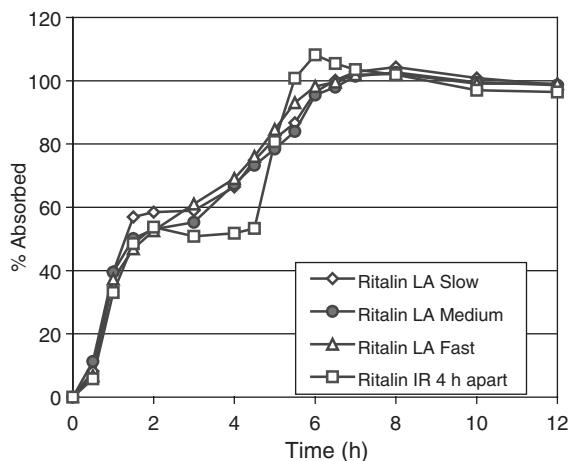


Figure 3. Cumulative fraction of MPH absorbed from Ritalin LA slow-, medium- and fast-release formulations and from Ritalin-IR tablet given 4 h apart

time) for the release of MPH from the DR beads. Because of limited samples taken during the initial dissolution period, accurate measurement

of the lag-time was not possible. Roughly, the release of MPH appeared to start rapidly without much delay when a low percentage of polymer was used, whereas the release was delayed significantly for the medium- and fast-release formulations. However, the lag-time difference among the three Ritalin LA formulations was not apparent in the plasma concentration-time profiles and in the *in vivo* absorption-time profiles obtained by deconvolution (between ~3–6 h). The apparent lack of *in vitro* to *in vivo* correlation (IVIVC) for the lag-time among different Ritalin LA formulations was probably related to the mechanism of drug release from the DR beads, the difference in dissolution medium between *in vitro* and *in vivo*, and the pre-existence of MPH in plasma resulting from the IR beads.

MPH is a small molecule, MW 269.8, and it is freely soluble in water. At physiological pH, the octanol/water partition coefficient is low, ~0.07; however, this fraction is sufficiently high to permeate biological membranes [17,18]. As shown in the deconvolution profile, the fraction absorbed increases rapidly between ~0–2 h and relatively slowly between ~3–6 h. This biphasic absorption phenomenon seems well correlated with the bimodal release characteristics of Ritalin LA, with the rapid absorption phase and somewhat slower absorption phase being roughly correlated with the release of MPH from the IR beads and the DR beads. The release of MPH from the DR beads most likely takes place in the middle and/or lower GI regions where the pH is neutral. At the neutral pH, the polymethacrylate polymer erodes slowly while allowing water to penetrate and dissolve MPH for subsequent diffusion out of the matrix. An increased erosion process for the polymer would diminish the dissolution differences among different formulations for the DR beads. Further studies on the dissolution and erosion process at different dissolution conditions mimicking the *in vivo* environment are warranted. Although the exact mechanism for the lack of lag-time difference *in vivo* is still unclear, the study results suggest that some changes in the dissolution profiles for the DR beads within the range being tested *in vitro* will have minimal impact on the *in vivo* absorption and plasma concentration-time profiles.

The comparison between Ritalin LA slow-, medium- and fast-release formulations revealed an equivalent rate and extent of absorption based on the primary pharmacokinetic parameters $C_{\max(\text{abs})}$, $t_{\max(\text{abs})}$, AUC_{0-t} and $AUC_{0-\infty}$ and the secondary PK parameters describing the bimodal characteristics; i.e. $C_{\max(0-4)}$, $t_{\max(0-4)}$ and AUC_{0-4} for the first peak and $C_{\max(4-8)}$, $t_{\max(4-8)}$ and AUC_{4-8} for the second peak. Therefore, based on the primary and secondary PK parameters, the three Ritalin LA formulations with different *in vitro* dissolution profiles were considered to be bioequivalent to one another.

Comparing the concentration-time profiles between the Ritalin LA capsule (medium-release formulation) and the Ritalin IR tablet, the rate and extent of absorption of MPH from the IR beads of Ritalin LA formulation ($C_{\max(0-4)}$, $t_{\max(0-4)}$ and AUC_{0-4}) were similar to those of the Ritalin IR tablets (1st tablet). However, the rate of absorption (based on $C_{\max(4-8)}$) from the DR beads of the Ritalin LA formulation was found to be significantly lower than that from the Ritalin IR 2nd tablet dosed 4 h later. Comparing the minimum concentration between peaks ($C_{\min p}$), it was found that the $C_{\min p}$ value for the Ritalin LA formulation was significantly higher than that of Ritalin IR tablets given 4 h apart. A lower $C_{\max(4-8)}$ value and a higher $C_{\min p}$ value for Ritalin LA compared with Ritalin IR tablets resulted in similar AUC values at the second peak for both formulations. On the other hand, a lower $C_{\max(4-8)}$ value and a higher $C_{\min p}$ value for Ritalin LA resulted in a lower fluctuation of MPH concentrations than for Ritalin IR tablets over the first 8 or 10 h period. Since the AUC values for the first and second peaks were similar for Ritalin LA and Ritalin IR, the overall extent of exposure ($AUC_{0-\infty}$ or AUC_{0-t}) was similar for both formulations. The bioavailability of Ritalin LA slow-, medium- and fast-release formulations relative to Ritalin IR was $97.3 \pm 14.1\%$, $97.0 \pm 12.6\%$ and $101.2 \pm 13.8\%$, respectively. The terminal elimination half-life of MPH was similar for Ritalin LA and Ritalin IR formulations, ~3–3.5 h.

In conclusion, the bimodal release Ritalin LA formulation demonstrated unique dissolution and absorption-time profiles, with 50% of the dose being released and absorbed rapidly and

the other 50% being released slowly at a later time acting as a second dose. The initial rate and overall extent of absorption of MPH from Ritalin LA were similar to those from Ritalin IR formulation given b.i.d. 4 h apart, but with less fluctuation in plasma concentration than the IR formulation. The *in vivo* absorption of MPH from the three Ritalin LA formulations was similar, suggesting that some changes in the *in vitro* dissolution profiles for the DR beads within the range being tested in the present study would have minimal impact on the *in vivo* absorption and plasma concentration-time profiles of MPH in humans.

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