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(54) **Title:** EFFECTIVE DOSING OF A CHILD FOR THE TREATMENT OF ADHD WITH METHYLPHENIDATE

(57) **Abstract:** The present invention generally relates to treating attention-deficit disorders (e.g., ADHD) by providing an effective amount of an ADHD-effective agent to a patient in need thereof (e.g., a child).

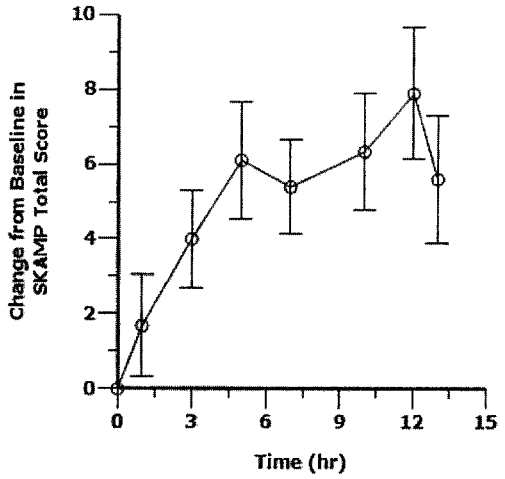

Figure 1

WO 2018/085256 A1

EFFECTIVE DOSING OF A CHILD FOR THE TREATMENT OF ADHD WITH METHYLPHENIDATE

FIELD OF INVENTION

[0001] The present invention generally relates to treating attention-deficit disorders (e.g., ADHD) by providing an effective amount of an ADHD-effective agent to a patient in need thereof (e.g., a child).

BACKGROUND OF INVENTION

Field of the Invention

[0002] The invention relates to the treatment of Attention Deficit Hyperactivity Disorder (ADHD) by providing an effective amount of a dosage form. In particular, the invention provides a method for determining an effective amount of a methylphenidate formulation for administration to an individual.

Description of the Related Art

[0003] Many drug therapies use immediate-release oral dosage forms administered at spaced intervals to provide and maintain a desired therapeutic effect over a prolonged therapy period. For example, drugs used in treating Attention Deficit Disorder (ADD) and ADHD such as ADDERALL® and RITALIN® are administered two or three times a day.

[0004] For various reasons, subjects often experience difficulty complying with this administration schedule. Because ADD and ADHD are commonly diagnosed in children, determining the correct dose for individual patients is complicated by the variability in size as patients grow. The dosage regimen for children generally requires that at least one dose is administered during the school day. Children are typically not permitted to self-administer the drug at school. As such, authorized school personnel generally take on the responsibility for administering the drug to children during the school day. However, this approach raises issues of medical privacy and potential stigmatizing of the

child by peers. In addition, the compliance issue becomes further complicated as transportation, storage and supply of the drug typically must be documented and/or monitored, and the schedules of the different parties involved, i.e., the child, the educators and the authorized school personnel, must be coordinated and accommodated. The unfortunate result is that doses may be given late or missed altogether resulting in decreased efficacy of the therapy.

[0005] Additionally, an effective method of dosing of drug therapies is currently described in the art as "titrating to effect". As shown in the prescription label for Daytrana®: "Dosage should be titrated to effect. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient."

[0006] WO 2015/188092 describes that "the recommended dosing regimen begins with a titration regimen, starting the patient at a low dose for seven days, followed by weekly upward adjustments until the optimal response is reached." Additionally, the publication describes that "[i]t is known that clearance of methylphenidate is an important factor in reaching and maintaining therapeutically effective levels of MPH in a patient. However, it is also known that drug clearance in children and adults does not always correlate well with their total body weight." While the publication describes a dosing regimen for the specific formulation utilized, there is still a need for dosing regimens for other formulations of methylphenidate products.

SUMMARY OF EMBODIMENTS OF THE INVENTION

[0007] The present disclosure provides methods of treating a patient comprising administering an effective amount of a drug composition, wherein the effective amount of the drug composition is calculated based on a pharmacokinetic-pharmacodynamic correlation (PK-PD correlation). In one embodiment, the present disclosure provides for methods of treating a patient in need thereof (e.g.,

a child) with an effective amount of an oral composition that provides effective, prolonged treatment.

[0008] In one embodiment, the present disclosure provides methods of establishing an effective amount of a drug formulation for treating an individual patient (e.g., a child) in need of treatment for a disease (e.g., ADHD or ADD). In particular, the effective amount of the oral composition can be calculated for any individual patient in need thereof (e.g., a child) based on the PK-PD correlation. The PK-PD correlation for the drug formulation can be adjusted based on a predictive factor (e.g. the weight of the patient) as a representative adjustment factor to reduce error in the PK-PD correlation. The effective amount of the composition for the individual patient in need thereof (e.g., a child) may be administered once-a-day as a single or multiple unit dose.

[0009] In some embodiments, the effective amount of the drug formulation is calculated by: measuring serum concentration at various times after dose administration for each individual in a first test population for a pharmaceutical active component in a drug formulation, generating a serum concentration profile over time for the drug formulation using the measured serum concentrations for the first test population by determining several pharmacokinetic parameters and the values of the several pharmacokinetic parameters by fitting the measured concentration values to generate a serum concentration profile, generating a pharmacokinetic equation for the drug formulation comprising the determined pharmacokinetic parameters and values, measuring a pharmacodynamic effect of the active component in the drug formulation at various times in a second test population, calculating a predicted serum concentration of the active component in the drug formulation in the second test population based on the generated pharmacokinetic equation, fitting the generated data of the pharmacodynamic effect and the predicted pharmacokinetic effect for each point in time to produce a pharmacokinetic-pharmacodynamic (PK-PD) correlation, and using the PK-PD correlation to generate a dosage chart that specifies the effective amount of the

drug formulation. Presentation of the dosage information in alternative formats, such as a mobile telephone app, a website, an electronic patient care software, etc., is within the contemplation of this disclosure.

[0010] In some embodiments, the calculation of the predicted serum concentration of the active component in the drug formulation in the second test population based on the generated pharmacokinetic equation and the measuring of the pharmacodynamic effect of the active component in the drug formulation are used to produce a PK-PD correlation.

[0011] In some embodiments, one or more predictive factors can be included in the PK-PD correlation of the drug formulation as a representative adjustment factor to reduce error in the PK-PD correlation. In one embodiment, the predictive factor is the weight of the individual patient.

[0012] In some embodiments, the dosage chart is a printed or digital dosage chart that provides the effective amount of the dosage form for particular patients or groups of patients. In some embodiments, a physician is able to predict the effective dosage for an individual patient by consulting a dosage chart.

[0013] In some embodiments, the *in vivo* serum profiles of the composition are correlated to the *in vitro* dissolution profile of the composition. In another embodiment, a physician is able to predict the *in vivo* serum profile by the *in vitro* dissolution profile of the composition, when the weight of the patient is considered for dosing.

[0013A] In some embodiments, the present invention provides a method of treating attention deficit hyperactivity disorder (ADHD) in an individual patient comprising administering to said individual patient a therapeutically effective amount for said patient of an oral dose form containing an ADHD-effective agent,

wherein the oral dose form has an in vitro release profile of: 30-33% of the ADHD-effective agent is released within the first 30 minutes after the oral dose form is introduced into an in vitro dissolution assay, 34-42% of the agent is released within 2 hours, 40-80% of the agent is released within 4 hours, and 80-100% of the agent is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follow:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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[0013B] In some embodiments, the present invention provides the use of an attention deficit hyperactivity disorder (ADHD)-effective agent in the manufacture of a medicament for treating ADHD in an individual patient,

wherein the medicament is provided in an oral dose form that has an in vitro release profile of: 30-33% of the ADHD-effective agent is released within the first 30 minutes after the oral dose form is introduced into an in vitro dissolution assay, 34-42% of the agent is released within 2 hours, 40-80% of the agent is released within 4 hours, and 80-100% of the agent is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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[0013C] In some embodiments, the present invention provides a method of treating attention deficit hyperactivity disorder (ADHD) comprising administering to an individual patient a therapeutically effective amount for said individual patient of an oral dose form containing an ADHD-effective agent, wherein, for *in vivo* pharmacokinetic parameters of the composition, at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ has a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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[0013D] In some embodiments, the present invention provides the use of an attention deficit hyperactivity disorder (ADHD)-effective agent in the manufacture of a medicament for treating ADHD in an individual patient,

wherein the medicament is provided in an oral dose form,

wherein for *in vivo* pharmacokinetic parameters of the medicament, at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ has a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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[0013E] In some embodiments, the present invention provides a method of assisting a physician in prescribing a dose of methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in an individual patient, comprising:

a. determining the body weight of said individual patient;

b. referring to a chart or reference tool that correlates a plurality of body weight ranges with a corresponding number of dosage amounts each having a different level of methylphenidate; and

c. identifying a single dosage amount corresponding to a particular weight range in which said individual patient's weight falls in the chart or reference tool,

wherein the chart or reference tool includes the following correlations between body weight range and said dosage amount of methylphenidate hydrochloride equivalent:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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wherein the methylphenidate is formulated in a composition having an *in vitro* release profile of: 30-33% of the methylphenidate is released within the first 30 minutes after the oral dose form is introduced into an *in vitro* dissolution assay, 34-42% of the methylphenidate is released within 2 hours, 40-80% of the methylphenidate is released within 4 hours, and 80-100% of the methylphenidate is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2, and/or

wherein the methylphenidate is formulated in a composition that produces an *in vivo* release profile having at least one in vivo pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ having a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition.

[0013F] In some embodiments, the present invention provides a method of treating attention deficit hyperactivity disorder (ADHD) in an individual patient, comprising:

a. determining the body weight of said individual patient;

b. referring to a chart or reference tool that correlates a plurality of body weight ranges with a corresponding number of dosage amounts each having a different level of methylphenidate;

c. identifying a single dosage amount corresponding to a particular weight range in which said individual patient's weight falls in the chart or reference tool; and

d. administering to said individual patient the identified dosage amount,

wherein the chart or reference tool includes the following correlations between body weight range and said dosage amount of methylphenidate hydrochloride equivalent:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

,

wherein the methylphenidate is formulated in a composition having an *in vitro* release profile of: 30-33% of the methylphenidate is released within the first 30 minutes after the oral dose form is introduced into an *in vitro* dissolution assay, 34-42% of the methylphenidate is released within 2 hours, 40-80% of the methylphenidate is released within 4 hours, and 80-100% of the methylphenidate is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2, and/or

wherein the methylphenidate is formulated in a composition that produces an *in vivo* release profile having at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ having a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

DEFINITIONS

[0013G] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[0013H] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each of the appended claims.

[0014] As used herein, an "ADHD effective agent" is any agent effective to treat ADHD or ADD in any patient population (e.g., children, adolescents, adults), wherein the agent includes stimulants such as methylphenidate, and its optical isomers, or any combination that comprises at least one of these agents. As discussed herein, ADHD effective agents may also be used in the effective treatment of other conditions such as fatigue, obesity and for imparting alertness.

[0015] As used herein, an "effective amount" of the ADHD effective agent (e.g., methylphenidate) is an amount that, when administered to a patient in need, provides the desired effect on the disease pathophysiology.

[0016] As used herein, a "reference composition" is a product defined in any relevant example from WO 2013/003622 A1, which is incorporated herein by reference.

[0016A] Examples of reference compositions as described in relevant examples from WO 2013/003622 A1 are set out in the following paragraphs.

Example 17 - Orally Disintegrating Tablet with 25% IR and 75% ER/DR

[0016B] An orally disintegrating tablet was formulated with 25% of methylphenidate from immediate release resin complex and 75% of the methylphenidate from an extended release (ER)/delayed release (DR) resin complex. In the ER/DR coating, ethylcellulose overlays Eudragit. The formula is presented below.

[0016C] Table 18: ODT methylphenidate Formulation A with 25% IR and 75% ER/DR.

IR Resin - 36.98% base assay & ER/DR Resin - 13.1 1% base assay: These values are variable.

	Formula A (25% active from IR Resin & 75% active from ER/DR Resin)		
	mg / dose	Notes	%
Uncoated (IR) MPH Resin	**17.65**	The 17.65 mg / dose quantity is the actual amount of IR resin (at a 36.98% assay value) that goes into each tablet. The values in the gray area are the quantities of each material that compromise the IR material.	**2.67**
Methylphenidate (base)	6.525		
Amberlite IRP069 Resin	10.24		
Polyethylene Glycol	0.441		
Purified Water	0.441		
Coated (ER/DR) MPH Resin	**149.37**	The 149.37 mg / dose quantity is the actual amount of ER/DR resin (at a 13.11% assay value) that goes into each tablet. The IR resin material was used to make the 149.37 mg / dose ER/DR material. The values in the gray area are the quantities of each material that compromise the ER/DR material.	**22.63**
Methylphenidate (base)	19.575		
Amberlite IRP069 Resin	30.72		
Polyethylene Glycol	1.32		
Purified Water	1.32		
Ethylcellulose N-10	11.505		
Eudragit L100	73.37		
Triethyl Citrate	11.56		
Prosolv ODT	**369.83**	The Prosolv ODT quantity will be variable to account for the variable assay value of the IR and DR resin.	**56.03**
Crospovidone	**66.00**		**10.00**
Sucralose Powder	**23.00**		**3.48**
Citric Acid	**10.00**		**1.52**
Natural Masking Agent	**8.00**		**1.21**
Natural Creamy Grape	**8.00**		**1.21**
Lake Blend Purple	**1.55**		**0.24**
Magnesium Stearate	**6.60**		**1.00**
Total	660.00 mg		100%

[0016D] Table 19: ODT methylphenidate Formulation B with 25% IR and 75% F/R/DR.

IR Resin - 36.98% base assay & ER/DR Resin - 12.77% base assay: These values are variable.

	Formula B (25% active from IR Resin & 75% active from ER/DR Resin)		
	mg / dose	Notes	%
Uncoated (IR) MPH Resin	**17.65**	The 17.65 mg / dose quantity is the actual amount of IR resin (at a 36.98% assay value) that goes into each tablet. The values in the gray area are the quantities of each material that compromise the IR material.	**2.67**
Methylphenidate (base)	6.525		
Amberlite IRP069 Resin	10.24		
Polyethylene Glycol	0.441		
Purified Water	0.441		
Coated (ER/DR) MPH Resin	**153.32**	The 153.32 mg / dose quantity is the actual amount of ER/DR resin (at a 12.77% assay value) that goes into each tablet. The IR resin material was used to make the 153.32 mg / dose ER/DR material. The values in the gray area are the quantities of each material that compromise the ER/DR material.	**23.23**
Methylphenidate (base)	19.575		
Amberlite IRP069 Resin	30.72		
Polyethylene Glycol	1.32		
Purified Water	1.32		
Ethylcellulose N-10	13.13		
Eudragit L100	75.31		
Triethyl Citrate	11.945		
Prosolv ODT	**365.88**	The Prosolv ODT quantity will be variable to account for the variable assay value of the IR and DR resin.	**55.44**
Crospovidone	**66.00**		**10.00**
Sucralose Powder	**23.00**		**3.48**
Citric Acid	**10.00**		**1.52**
Natural Masking Agent	**8.00**		**1.21**
Natural Creamy Grape	**8.00**		**1.21**
Lake Blend Purple	**1.55**		**0.24**
Magnesium Stearate	**6.60**		**1.00**
Total	660.00 mg		100%

[0016E] These formulas are exactly the same except for the level of actual ethylcellulose coating (as determined by assay). Formula "A" has 18.6% ethylcellulose coating and "B" has 20.7%. These are the calculated coating levels of ethylcellulose prior to the eudragit coating.

Dissolution Method

[0016F] Dissolution testing is carried out using an Apparatus 2 with cannulas and cannula filters (Quality Lab Accessories, Porus Micron full flow filters 20 micron); paddle speed - 100 rpm; kettle size- 1000 mL; temperature - 37.0±0.5°C; filter - 25mm 0.45µm PTFE; syringe - B-D10 ml. Luer-Lok.

Dissolution Media:

[0016G] The medium for the dissolution assay is 900 mL of 0.1N HQ for the first hour; after 2 hour time point ~100mL of potassium phosphate/Sodium Hydroxide solution is added to bring to pH ~ 6.8.

[0016H] The sample is weighed and is placed into the corresponding kettle, and the dissolution timing started.

[0016I] Sampling pull times are 30 minutes, 2 hours, 4 hours and 8 hours. For each sample pull time and each kettle, 10mL of sample are pulled into a B-D 10 mL Luer-Lok syringe and returned to the kettles before the sample pull to flush out the cannula from the prior pulls. 4ml are then pulled for filtration, discarding the first 2 ml to waste and the remaining sample into an HPLC vial. Non-media replacement and volume changes from the two media changes are calculated.

Dissolution Profile:

[0016J] The amount of drug in the filtrate at each time point is determined by HPLC, and the percentage released from Formulae A and B, respectively, are shown below and in Figure 26.

[0016K] Formula A Profile e)

Hours	Profile (%Release)
0.5	31%
2	39%
4	79%
8	87%
24	87%

[0016L] Formula B Profile e)

Hours	Profile (%Release)
0.5	32%
2	41%
4	80%
8	90%
24	90%

Example 18 - Human Pharmacokinetic Study Using OPT Pharmaceutical Compositions

[0016M] This example describes a single-dose, open-label, randomized, three-period, three-treatment crossover study comparing the rate of absorption and oral bioavailability of two controlled release ODT preparations of methylphenidate polistirex (equivalent to 60 mg methylphenidate) to an equivalent 60 mg oral dose of the commercially available reference product, Metadate CD®, (UCB, Inc.) following an overnight fast of at least 10 hours. Subjects were randomly assigned to a treatment sequence and received three, separate single-dose administrations of study medication, one treatment per period, according to the randomization schedule. Dosing days were separated by a washout period of at least 7 days.

[0016N] Subjects received each of the treatments listed below during the three treatment periods:

[0016O] Treatment A: Test Formulation #1 (methylphenidate resins) controlled-release ODT. Test Formulation #1 is substantially similar to the formulation A described in Example 17. Dose = 2 x methylphenidate polistirex ODT containing 26.1 mg methylphenidate base, equivalent to 60 mg methylphenidate HCl.

[0016P] Treatment B: Test Formulation #2 (methylphenidate resins) controllcd-release ODT. Test Formulation #2 is substantially similar to the formulation B described in Example 17. Dose = 2 x

methylphenidate polistirex ODT containing 26.1 mg methylphenidate base, equivalent to 60 mg methylphenidate HCl.

[0016Q] Treatment C: Reference Product Metadate CD® UCB, Inc. Dose = 1 x 60 mg capsule

Clinical Procedures Summary

[0016R] During each study period, 6 mL blood samples were obtained prior to each dosing and following each dose at selected times through 36 hours post-dose. A total of 63 pharmacokinetic blood samples were collected from each subject, 21 samples in each study period. In addition, blood was drawn and urine was collected for clinical laboratory testing at screening and study exit.

[0016S] In each study period, subjects were admitted to the study unit in the evening prior to the scheduled dose. Subjects were confined to the research center during each study period until completion of the 24-hour blood collection and other study procedures. Subjects returned to the study unit for outpatient pharmacokinetic blood samples at 36 hours. Thirty-eight (38) of the 42 subjects enrolled completed the study.

Procedures for Collecting Samples for Pharmacokinetic Analysis

[0016T] Blood samples (1 x 6 ml.) were collected in vacutainer tubes containing K_2-EDTA as a preservative at pre-dose (0) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 18.0, 24.0, and 36.0 hours after dosing.

Bioanalytical Summary

[0016U] Plasma samples were analyzed for d-methylphenidate and 1-methylphenidate by a third party laboratory using a validated LC-MS-MS procedure. The method was validated for a range of 0.250 to 50.0 ng/mL for d-methylphenidate and 0.0100 to 2.00 ng/mL for 1-methylphenidate, based on the analysis of 0.100 mL of human EDTA plasma.

Pharmacokinetic Analysis

[0016V] Concentration time data were analyzed by noncompartmental methods in WinNonlin. Concentration time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.

[0016W] The following pharmacokinetic parameters were calculated for d-methylphenidate, l-methylphenidate, and total methylphenidate (d + 1): peak concentration in plasma (Cmax), time to peak concentration (Tmax), elimination rate constant (λz), terminal half-life (T1/2), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUClast), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUCinf). Secondary pharmacokinetic endpoints included partial AUCs. The following partial AUCs were calculated using the linear trapezoidal method: AUC0-3, AUC0-tmax (AUC0-5), AUCtmax-24 (AUC5-24), AUC0-24, and AUCtmax-tlast.

[0016X] Test Formulations #1 and #2 were compared to the reference product. Analysis of variance (ANOVA) and the Schuirmann's two one sided t test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, Cmax, AUClast, and AUCinf d-methylphenidate, l-methylphenidate, and total methylphenidate (d + 1). The 90% confidence interval tor the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%. mComparisons of partial AUCs, AUC0-3, AUC0-tmax (AUC0-5), AUCtmax-24 (AUC5-24), AUC0-24, and AUCrmax-tlast across treatments were performed as supportive evidence of equivalence.

Results

[0016Y] Data from 38 subjects who completed the study were included in the pharmacokinetic and statistical analyses.

[0016Z] Figures 20A and 20B show the mean linear and log d-methylphenidate concentration- time profiles after administration of Test Formulation #1 (Treatment A), Test Formulation #2 (Treatment B), and Reference Product (Treatment C).

[0016AA] Figures 21A and 21B show the mean linear and log 1-methylphenidate concentration-time profiles after administration of Test Formulation #1 (Treatment A), Test Formulation #2 (Treatment B), and Reference Product (Treatment C).

[0016AB] Figures 22A and 22B show the mean linear and log total methylphenidate (d + 1) concentration-rime profiles after administration of Test Formulation #1 (Treatment A), Test Formulation #2 (Treatment B), and Reference Product (Treatment C).

[0016AC] Table 20: Statistical Analysis of the Log-transformed Systemic Exposure Parameters of *d*-Methylphenidate Comparing Test Formulation 1 (Treatment A) to the Reference Product (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	20.1714	16.3095	123.68	117.21	130.50	1.0000	14.10
$\ln(AUC_{0-3})$	20.5344	23.7682	86.39	79.10	94.36	0.9935	23.36
$\ln(AUC_{0-tmax})$[d]	50.1624	50.0850	100.15	93.53	107.25	0.9998	18.03
$\ln(AUC_{tmax-24})$[d]	103.8409	95.3024	108.96	104.11	114.04	1.0000	11.94
$\ln(AUC_{0-24})$	156.7217	146.3987	107.05	103.73	110.48	1.0000	8.25
$\ln(AUC_{tmax-dlast})$[d]	104.3909	100.4459	103.93	98.76	109.37	1.0000	13.39
$\ln(AUC_{last})$	157.4500	151.7064	103.79	100.26	107.44	1.0000	9.05
$\ln(AUC_{inf})$	161.1557	157.9722	102.02	98.78	105.35	1.0000	8.43

[a] Geometric Mean for the Test Formulation 1 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

[d] The median T_{max} of the Reference Product (5.00 hr) was used

[0016AD] Table 21: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-Methylphenidate Comparing Test Formulation 2 (Treatment B) to the Reference Product (Treatment C).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	20.4113	16.3095	125.15	118.62	132.04	1.0000	14.10
$\ln(AUC_{0-3})$	21.7843	23.7682	91.65	83.92	100.10	0.9936	23.36
$\ln(AUC_{0-tmax})$[d]	51.9061	50.0850	103.64	96.79	110.97	0.9998	18.03
$\ln(AUC_{tmax-24})$[d]	105.8856	95.3024	111.10	106.16	116.27	1.0000	11.94
$\ln(AUC_{0-24})$	160.7525	146.3987	109.80	106.40	113.31	1.0000	8.25
$\ln(AUC_{tmax-tlast})$[d]	106.3546	100.4459	105.88	100.62	111.42	1.0000	13.39
$\ln(AUC_{last})$	161.3617	151.7064	106.36	102.75	110.10	1.0000	9.05
$\ln(AUC_{inf})$	165.4229	157.9722	104.72	101.40	108.14	1.0000	8.43

[a] Geometric Mean for the Test Formulation 2 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d]The median T_{max} of the Reference Product (5.00 hr) was used

[0016AE] Table 22: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-Methylphenidate Comparing Test Formulation 1 (Treatment A) to the Reference Product (Treatment C).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	0.4471	0.2224	201.01	167.90	240.64	0.6550	49.75
$\ln(AUC_{0-3})$	0.6292	0.2691	233.82	198.86	274.92	0.7346	44.29
$\ln(AUC_{0-tmax})$[d]	1.0739	0.5281	203.35	175.47	235.66	0.8024	40.01
$\ln(AUC_{tmax-24})$[d]	0.9649	0.7668	125.84	108.56	145.87	0.8013	40.08
$\ln(AUC_{0-24})$	2.1909	1.3404	163.45	143.93	185.62	0.8936	34.18
$\ln(AUC_{tmax-tlast})$[d]	0.8821	0.7435	118.64	101.75	138.33	0.7736	41.81
$\ln(AUC_{last})$	2.1125	1.3231	159.66	140.14	181.90	0.8801	35.09
$\ln(AUC_{inf})$	2.2098	1.5598	141.68	122.06	164.44	0.7952	40.46

[a] Geometric Mean for the Test Formulation 1 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d]The median T_{max} of the Reference Product (5.00 hr) was used

[0016AF] Table 23: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *l*-Methylphenidate Comparing Test Formulation 2 (Treatment B) to the Reference Product (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	0.5092	0.2224	228.93	191.26	274.02	0.6557	49.75
$\ln(AUC_{0-3})$	0.6798	0.2691	252.63	214.89	296.99	0.7354	44.29
$\ln(AUC_{0-tmax})$[d]	1.1261	0.5281	213.23	184.02	247.07	0.8031	40.01
$\ln(AUC_{tmax-24})$[d]	1.1095	0.7668	144.70	124.85	167.70	0.8021	40.08
$\ln(AUC_{0-24})$	2.4426	1.3404	182.23	160.49	206.92	0.8942	34.18
$\ln(AUC_{tmax-tlast})$[d]	1.0239	0.7435	137.71	118.13	160.55	0.7744	41.81
$\ln(AUC_{last})$	2.3641	1.3231	178.68	156.86	203.54	0.8807	35.09
$\ln(AUC_{inf})$	2.4774	1.5598	158.83	136.87	184.32	0.7959	40.46

[a] Geometric Mean for the Test Formulation 2 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d]The median T_{max} of the Reference Product (5.00 hr) was used

[0016AG] Table 24: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Total Methylphenidate (*d* + *l*) Comparing Test Formulation 1 (Treatment A) to the Reference Product (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	20.6080	16.5477	124.54	117.98	131.46	1.0000	14.21
$\ln(AUC_{0-3})$	21.2961	24.1188	88.30	80.92	96.35	0.9943	23.10
$\ln(AUC_{0-tmax})$[d]	51.4307	50.7312	101.38	94.67	108.56	0.9998	18.02
$\ln(AUC_{tmax-24})$[d]	105.0763	96.2603	109.16	104.30	114.24	1.0000	11.94
$\ln(AUC_{0-24})$	159.2597	148.0008	107.61	104.29	111.03	1.0000	8.20
$\ln(AUC_{tmax-tlast})$[d]	105.6235	102.0912	103.46	98.33	108.86	1.0000	13.35
$\ln(AUC_{last})$	159.9855	153.9687	103.91	100.39	107.55	1.0000	9.03
$\ln(AUC_{inf})$	163.6833	159.5401	102.60	99.37	105.93	1.0000	8.36

[a] Geometric Mean for the Test Formulation 1 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d]The median T_{max} of the Reference Product (5.00 hr) was used

[0016AH] Table 25: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Total Methylphenidate (*d* + *l*) Comparing Test Formulation 2 (Treatment B) to the Reference Product (Treatment C).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	20.8467	16.5477	125.98	119.35	132.97	1.0000	14.21
$\ln(AUC_{0-3})$	22.5591	24.1188	93.53	85.73	102.05	0.9944	23.10
$\ln(AUC_{0-tmax})$[d]	53.1774	50.7312	104.82	97.90	112.24	0.9998	18.02
$\ln(AUC_{tmax-24})$[d]	107.4905	96.2603	111.67	106.70	116.86	1.0000	11.94
$\ln(AUC_{0-24})$	163.6952	148.0008	110.60	107.20	114.12	1.0000	8.20
$\ln(AUC_{tmax-tlast})$[d]	108.1238	102.0912	105.91	100.66	111.43	1.0000	13.35
$\ln(AUC_{last})$	164.4747	153.9687	106.82	103.21	110.57	1.0000	9.03
$\ln(AUC_{inf})$	168.3659	159.5401	105.53	102.22	108.95	1.0000	8.36

[a] Geometric Mean for the Test Formulation 2 (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d] The median T_{max} of the Reference Product (5.00 hr) was used

Conclusions

[0016AI] Based on C_{max}, the peak exposure to *d*-methylphenidate is higher after administration of Test Formulations 1 and 2 relative to that after Metadate CD® and the 90% confidence intervals about the ratios for C_{max} (Test Formulation 1/Reference and Test Formulation 2/Reference) are not within the 80% to 125% range necessary to establish traditional bioequivalence. However, based on AUC_{last} and AUC_{inf}, the overall systemic exposure to *d*-methylphenidate after administration of Test Formulations 1 and 2 is comparable to that after Metadate CD® and the 90% confidence intervals about the ratios for AUQ_{0-3} and AUC_{inf} are within the 80% to 125% range, indicating no significant difference in bioavailability. Except for AUC_{0-3} after Test Formulation 1 (ratio: 86.39%; 90% confidence interval: 79.10% - 94.36%), the 90% confidence intervals about the Test/Reference ratios for all partial AUCs are within the 80% to 125% range, indicating comparable early systemic

exposure through T_{max} (5.00 hr) and 24 hours after Test Formulations 1 and 2 relative to Metadate CD®.

[0016AJ] Based on C_{max}, AUC_{last}, and AUC_{inf}, peak and overall systemic exposure to *d*-methylphenidate is higher after administration of Test Formulations 1 and 2 relative to that after Metadate CD® and the 90% confidence intervals about the Test/Reference ratios (Test Formulation 1/Reference and Test Formulation 2/Reference) are not within the 80% to 125% range necessary to establish traditional bioequivalence. Similarly, based on partial AUCs, early systemic exposure to *d*-methylphenidate is higher after administration of Test Formulations 1 and 2 relative to that after Metadate CD® and the 90% confidence intervals about the Test/Reference ratios for all partial AUCs are not within the 80% to 125% range.

[0016AK] Based on AUC_{last} and AUC_{inf}, the overall systemic exposure to total methylphenidate (*d* + *l*) after administration of Test Formulations 1 and 2 is comparable to that after Metadate CD® and the 90% confidence intervals about the ratios for AUC_{last}, and AUC_{inf} are within the 80% to 125% range, indicating no significant difference in bioavailability. In addition, the 90% confidence intervals about the Test/Reference ratios for all partial AUCs are within the 80% to 125% range, indicating comparable early systemic exposure through 3 hours, T_{max} (5.00 hr), and 24 hours after Test Formulations 1 and 2 relative to Metadate CD®.

[0017] As used herein, "controlled release" means the time course of drug appearance in medium surrounding the composition is modified compared to an immediate release composition. Controlled release encompasses "delayed release" and "extended release" formulations.

[0018] As used herein, "delayed release" means that appearance of drug in the medium surrounding the composition occurs after a time lapse. An example of a delayed release coating is a triggered-release coating.

[0019] As used herein, a "triggered-release coating" is a coating that degrades as a result of a triggering event, where the triggering event is a change in the physiological environment of surrounding the triggered-release coating. Triggering events include, but are not limited to, a pH change which occurs upon transit from one stage to another stage in a subject's gastrointestinal (GI) tract, an enzyme secreted in a particular region in a subject's GI tract, or enzymatic presence in digestion.

[0020] As used herein, "extended release" means that the rate of release is slower than the rate for an immediate release or delayed release composition from the initial point of release.

[0021] As used herein, "immediate release" means the initial period during which drug is released from the composition that does not involve delayed or extended release but may include taste-masking.

[0022] As used herein, a "subject" means any animal, but is preferably a mammal, such as, for example, a human.

[0023] As used herein, "substantially all," in the context of drug release, means 90% or more.

[0024] As used herein, "substantially similar" parameters have values within −20%/+25% of each other.

BIOAVAILABILITY

[0025] Measures of bioavailability well known in the art include the area under the plasma concentration-time curve (AUC), the concentration maximum (C_{max}), and the time to C_{max} (T_{max}).

[0026] AUC is a measurement of the area under the plasma concentration-time curve (e.g., serum concentration profile), and is representative of the amount of drug absorbed following administration of a single dose of a drug (see Remington: The Science and Practice of Pharmacy, (Alfonso R. Gennaro ed. 2000), page 999).

[0027] C_{max} is the maximum plasma concentration achieved after oral drug administration (see Remington, page 999). An oral drug administration results in at least one C_{max}, but may result in more than one "peak plasma concentration" or "plasma concentration peak" (for example, following the administration of a pulsed dose formulation).

[0028] T_{max} is the amount of time necessary to achieve the C_{max} after oral drug administration, and is related to the rate of absorption of a drug (see Remington, page 999).

[0029] Bioequivalence can be measured by pharmacokinetic parameters such as, for example, AUC and C_{max}. According to the FDA, a product is bioequivalent to a reference product if the 90% confidence intervals of the relative mean AUC, C_{max}, and T_{max} of the test formulation are within 80% to 125% (−20%/+25%) of the reference formulation drug when administered in the fasting state. In alternative phrasing, bioequivalence is the absence of a significantly different rate and extent of absorption in the availability of the active ingredient when administered at the same dose under similar conditions. In a particular embodiment, bioequivalence may be established by comparing a test drug to a reference drug by comparing partial AUCs (e.g., over statistically or clinically relevant

time intervals). This bioequivalence measure based partial AUCs may be used alone or in combination with the bioequivalence measures discussed above.

DETERMINING AN EFFECTIVE AMOUNT OF A FORMULATION

[0030] Pharmacokinetics describes the appearance and disappearance of a drug in the patient's body; pharmacodynamics correlates the drug concentration at the site of action to the physiological effect. For both concepts, the time course after dosing is important. However, determining the effective amount of a drug formulation for a child at a given stage in the growth and development period requires determining the pharmacodynamics of the drug formulation for the child at the given stage of growth and development. More specifically, the relationship, or a correlation, between the pharmacokinetics (PK) and pharmacodynamics (PD) of a given drug formulation for the patient at the given stage of growth and development must be determined.

[0031] Traditional methods of determining the PK-PD correlation of a given drug formulation are by administering the drug formulation, and monitoring a large number of parameters in the patient. Pharmacokinetics are typically measured by drawing blood from the individual patients at several times, while monitoring the patients' pharmacodynamic results at the same times. For stimulants like ADHD medication, the pharmacodynamics results can be skewed due to the awareness and adrenaline responses associated with drug monitoring (e.g., the use of a needle to collect samples), especially in children.

[0032] The present invention relates to generating a dosage chart for an individual patient (e.g., child) by determining the pharmacokinetics of a drug formulation in a group of patients and, from that data, generating a predictive formula based on the drug dosage and the pharmacokinetic measurement over time elapsed since administration of the drug formulation. The pharmacodynamics of the drug formulation can then be measured for a group of patients, and the predictive formula for the pharmacokinetic measurement can be compared to the data from the

pharmacodynamic measurements. The group of patients used to gather the pharmacokinetic data may be different from the group of patients used to gather the pharmacodynamic data. The group of patients used to gather the pharmacokinetic data may be the same group of patients used to gather the pharmacodynamic data as long as the pharmacokinetic data is gathered at a separate time from the pharmacodynamic data.

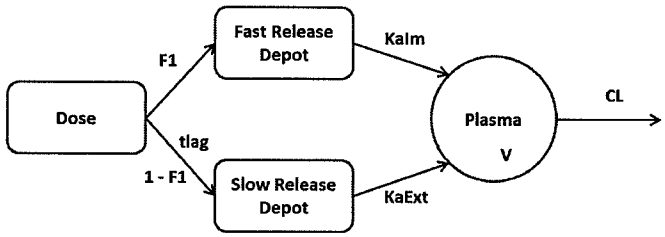
[0033] The PK-PD correlation of the drug formulation can be determined based on this comparison of the predictive formula for the pharmacokinetic measurement and the measured pharmacodynamic data over the same elapsed time since drug administration. This PK-PD correlation of the drug formulation can be used to calculate the dosing regimen for an individual patient. The dosing regimen for an individual patient may be based on predictive factors for the individual patient, such as height, weight, body mass index (BMI), volume of the systemic circulation, age, gender, etc.

[0034] The present disclosure provides for methods of determining an effective amount of a pharmaceutical methylphenidate formulation for administration to an individual (e.g., a child). If the methylphenidate formulation is being administered to a child, the ever-changing body volume of the child as the child grows can impact the effective amount of the methylphenidate formulation for that child at any given point in the growth period. Additionally, the relative activities of various enzyme systems can change over the growth and development of the child. Accordingly, in response to these changes, the drug dosage must be changed as the child grows and develops, to continue administering an effective amount of the drug for the child over time.

[0035] DETERMINING THE PHARMACOKINETICS

[0036] Developing a formula to predict the pharmacokinetics of the composition is complicated because the pharmacokinetics is determined by a large number of individualized characteristics as

the drug interacts with numerous different physiological entities in the body. However, surprisingly, the pharmacokinetics of the methylphenidate composition contemplated by this invention can be calculated by determining only a few parameters. Specifically, the pharmacokinetics of the methylphenidate composition can be adequately characterized using a PK model for methylphenidate plasma concentrations of compositions comprising an immediate release component and a controlled release component. Concentrations following administration of methylphenidate may be described by the following:



Where the parameters are the dose fraction absorbed via the immediate release component of the formulation (F1), the lag time of the controlled release component of the formulation (t_{lag}), the first-order rate constant for the immediate release component of the formulation (Ka_{Im}), the first-order rate constant for the controlled release component of the formulation (Ka_{Ext}), the apparent volume of methylphenidate distribution (V) and the apparent plasma clearance of methylphenidate (CL).

[0036] First-order elimination of methylphenidate from the central compartment adequately describes the elimination kinetics of methylphenidate from the plasma of human subjects. This elimination process can be described with a volume of distribution (V) and clearance (CL).

[0037] The selection of parameters and calculation of values for the parameters can be determined by measuring a serum concentration for each individual in a test population, and then fitting the serum concentration time data to a PK model using a nonlinear mixed-effects modeling program

with first-order conditional maximum likelihood estimation to find the best set of parameter values for the observed data.

[0038] An equation developed from the structural model shown above can be determined using patient data as discussed above to describe the pharmacokinetics of the drug compositions of this invention. The pharmacokinetics of the formulation can, therefore, be calculated using only a relatively small number of parameters.

MEASURING THE PHARMACODYNAMICS

[0039] The pharmacodynamics of the formulation can be determined using methods known to one of ordinary skill in the art, such as determining SKAMP, and/or PERMP scores at various times after administration of the test formulation. SKAMP scores are described in Wigal et al., *Effect of Reinforcement on Facial Responsivity and Persistence in Children with Attention-Deficit Hyperactivity Disorder*, Behavior Modification (April 1998), Vol. 22, No. 2, pp. 143–166, incorporated herein in its entirety. PERMP scores are described in Wigal et al., *Randomized, Double-Blind, Placebo-Controlled, Crossover Study of the Efficacy and Safety of Lisdexamfetamine Dimesylate in Adults with Attention-Deficit/Hyperactivity Disorder: Novel Findings Using a Simulated Adult Workplace Environment Design*, Behavioral and Brain Functions (2010), Vol. 6, p. 34, incorporated herein in its entirety.

CORRELATING THE PHARMACOKINETICS AND THE PHARMACODYNAMICS

[0040] In the present invention, the determination of the pharmacokinetics and the determination of the pharmacodynamics of a drug formulation do not need to be done at the same time, or on the same patient population. By not needing to take blood samples of the patients over a period of time, while studying the pharmacodynamic data, to determine the pharmacokinetics of the composition, the PK-PD correlation is not artificially skewed (e.g., by the sampling bias related to a needle producing artificial adrenaline responses).

GENERATING A DOSING REGIMEN

[0041] A dosing regimen can be generated based on a PK-PD correlation for any of the drug formulations described herein by: measuring serum concentration at various times after dose administration for each individual in a first test population for a pharmaceutical active component in a drug formulation, generating a pharmacokinetic equation describing the serum concentration profile for the drug formulation where the pharmacokinetic equation is characterized by several pharmacokinetic parameters determined by fitting the pharmacokinetic equation to the measured serum concentrations for the first test population, measuring a pharmacodynamic effect of the active component in the drug formulation at various times in a second test population, calculating a predicted serum concentration of the active component in the drug formulation in the second test population based on the generated pharmacokinetic equation, fitting the generated data of the pharmacodynamic effect and the predicted serum concentrations for each point in time to produce a PK-PD correlation, and generating a dosage chart describing the effective amount of the drug formulation.

[0042] In one embodiment, the drug formulation contains methylphenidate, and, optionally, an ion-resin.

[0043] In some embodiments, the first test population and the second test population comprise different individual subjects. The measurement of the serum concentration can be done at a different time than the measurement of the pharmacodynamic effect.

[0044] In one embodiment of the present disclosure, the PK-PD correlation is further predictive of the effective amount of the composition for an individual patient in need thereof (e.g., a child) when a predictive factor is included in the calculation as a representative adjustment factor to reduce error in the PK-PD correlation. When the composition comprises methylphenidate, the predictive factor can be on or more of a patient's weight, a patient's sex, a patient's age, or systemic volume. In children,

surprisingly, the predictive factor of weight alone was sufficient to adequately reduce the error in the PK-PD correlation (without needing to factor in other covariates such as body-mass index (BMI), sex, age, etc.).

[0045] In some embodiments, the physician can establish a dosing regimen for an individual patient based on the PK-PD correlation, and, optionally, based on the predictive factor for the individual patient. The dosing regimen for an individual patient can be individualized by one or more predictive factors for that individual patient. In a particular embodiment, the physician administers to a patient an effective amount of a formulation that provides the *in vivo* release profiles described herein, wherein the effective amount is based on the PK-PD correlation and a predictive factor, wherein the predictive factor is the patient's weight, the patient's age, or a combination of the patient's weight and sex.

[0046] In some embodiments, a dosage chart can be formulated using the methods described herein. In one embodiment, a dosage chart can be formulated by determining the pharmacokinetics of a formulation (e.g., calculating F1, t_{lag}, Ka_{Im}, Ka_{Ext}, V, and CL), determining the pharmacodynamics of the formulation (e.g., measuring the SKAMP or PERMP scores), generating a PK-PD correlation based on a predictive factor (e.g., weight of the individual patient), and determining the effective dose for an individual patient based on the output.

[0047] In some embodiments, the chart may describe the amount of methylphenidate hydrochloride equivalent in relation to the body weight of the patient. A physician can consult the chart to provide an effective amount of the drug formulation to administer to the patient based on the body weight of the patient. The dosage chart can be contained in various mediums, including paper, digital storage media, eInk, etc.

[0048] In some embodiments, the pharmacodynamic measurement is a psychological measurement, that may relate to measuring pain, sleep, attention, impotence, or measurements related to disorders of the central nervous system.

[0049] In some embodiments, a patient in need thereof (e.g., a child) is provided with an effective amount of an ADHD-effective agent in accordance with a dosage chart. In some embodiments, the patient in need thereof (e.g., the child) is provided with an effective amount of the formulation based on the following table:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

[0050] In some embodiments, a physician may prescribe a dose of methylphenidate for a patient in need thereof (e.g., a child) for the treatment of ADHD by: determining the body weight of the patient, referring to the chart above that correlates body weight ranges with a number of dosage amounts having a different level of methylphenidate, identifying the corresponding dosage amount to the body weight of the patient, and administering to the patient the dosage amount.

[0051] The present disclosure provides for methods of treating a patient in need thereof (e.g., a child) with an effective amount of an ADHD-effective agent (e.g., methylphenidate) where the ADHD-effective agent is formulated to provide the *in vivo* release profile described herein. Methylphenidate formulations which have *in vivo* release profiles suitable for the present invention

are described in one or more of the following: U.S. Pat. Nos. 4,221,778; 4,996,047; 5,980,882; 6,605,300; 6,913,768; 8,846,100; 6,344,215; 8,747,902; 8,465,765; 8,999,386; 8,883,213; 6,930,129; 6,228,398; 6,673,367; and 6,419,960; U.S. Publication Nos. 2003/0099711; 2006/0193877; 2007/0059270; 2007/01400983; 2007/0148239; US 2007/0264323; and 2009/0011027. The disclosure of each of these patents and publications is incorporated by reference herein in their entireties.

[0052] The present disclosure provides methods of treating a patient in need thereof (e.g., a child) with compositions having various drug (e.g., ADHD effective agent) release profiles. In particular, the compositions may be administered in the morning and have therapeutically effective activity throughout the course of the day. For example, in one embodiment, the composition is administered to a child during breakfast (i.e., before school starts) and, by the time school starts, the ADHD effective agent (e.g., methylphenidate) will begin having a therapeutic effect on the child. The composition will continue to be therapeutically effective throughout the day including the mid-afternoon, when children tend to be fatigued. As such, the compositions described herein typically have an escalating *in vivo* serum profile early in the therapeutic time course.

[0053] In one embodiment, the patient in need thereof (e.g., a child) is administered a composition having an *in vivo* serum profile bioequivalent to the profile of a reference composition. In another other embodiment, the composition has one or more parameters (e.g., at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or eleven parameters) selected from AUC_{0-4}, AUC_{0-5}, AUC_{4-12}, AUC_{5-12}, AUC_{5-t}(AUC_{5-last}), AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and/or T_{max} which meet the bioequivalence conditions for a reference composition.

[0054] In some embodiments, the present disclosure provides for methods of treating a patient in need thereof (e.g., a child) by providing compositions in which the rate of appearance of the ADHD

effective agent (e.g., methylphenidate) in a dissolution medium increases after a period of decrease in the rate of appearance of the drug in the dissolution medium. The compositions typically contain an immediate release and delayed release portion. The immediate release portion, in an *in vitro* dissolution assay, contributes to an initial release of ADHD effective agent (e.g., 30-60%) within an initial time period (e.g., 0.5, 1, 1.5, 2, or 2.25 hours from when the composition is introduced into the dissolution medium). After the initial increase amount of ADHD effective agent in the dissolution, due to the immediate release portion, the release rate of ADHD effective agent will decrease or level off. After this decrease or leveling off, typically the delayed release portion will release and the amount of ADHD effective agent released increases until, e.g., 80% or more of the ADHD effective agent is released. It will be appreciated that the first and second time points will vary depending on the ADHD effective agent, coatings used, and ratio of immediate and delayed release components of the composition.

[0055] In a particular embodiment, 30-33% of the drug (e.g., ADHD effective agent such as methylphenidate) is released the first 30 minutes after the composition is introduced into a dissolution assay, 34-42% of the drug is released within 30 minutes to 2 hours, 40-80% of the drug is released within 2 to 4 hours and 80-100% of the drug is released within 4 to 24 hours. For any of these embodiments, the conditions of the dissolution assay may be an initial dissolution medium of 0.1 NHCL, and after 2 hours, the medium is adjusted to a pH which triggers the triggered release coating, e.g., pH of ~6.8; and dissolution testing is performed using a USP Apparatus 2. In other embodiments, the pH is adjusted to e.g., pH 6.8, 7, etc.

[0056] The present disclosure also provides for methods of treating a patient in need thereof (e.g., a child) by providing compositions in which the composition achieves an ascending plasma concentration of the drug (e.g., methylphenidate during a time period) after a therapeutically effective level is reached. Typically, a therapeutically effective level is reached within one, two, or three hours after ingestion of the composition. Sometime after the therapeutically effective level is reached, the plasma

concentration of drug increases due to additional release of drug from the composition to a peak drug concentration level. In some individuals, clearance of drug will result in a decrease in plasma level between these two releases, resulting in two successive peak drug levels. In others, the timing of the two releases is close enough that no decrease is observed. As a result, the *in vivo* plasma concentration profile is preferably bimodal with two peaks. For example, the first peak may be achieved, between 1 to 3, 1 to 2.5, or 1 to 2 hours after ingestion of the composition. The second peak may be achieved 4 to 7, 4 to 6, or 4 to 5 hours after ingestion of the composition. The first or second peak may be the C_{max}. Alternatively, the composition may have an *in vivo* serum profile that reaches a therapeutically effective level fairly rapidly (1-3 hours) and them continues to increase more slowly up to a maximum serum level between 4 hours and 7 hours after ingestion. It will be appreciated that the therapeutic and peak drug concentration level will vary depending on the subject, drug, coatings used, and ratio of coatings.

[0057] The compositions administered to the patient in need thereof (e.g., a child) may include various coatings and components (e.g., particles coated with a delayed release coating, particles coated with an extended release coating, particles coated with an sustained release coating, etc.).

[0058] The formulation that provides the *in vivo* release profiles described herein may include components of any of the following: a delayed release component (e.g., contains delayed release coating), an immediate release component (e.g, an uncoated component), an extended release component, a sustained release component (e.g., comprising a water-insoluble, water-impermeable, pH independent, barrier coated ion-exchange resin complex), a modified release component (e.g., comprising a matrix), or combinations thereof. Suitable formulations are described in U.S. Pat. Nos. 4,221,778; 4,996,047; 5,980,882; 6,605,300; 6,913,768; 8,846,100; 6,344,215; 8,747,902; 8,465,765; 8,999,386; 8,883,213; 6,930,129; 6,228,398; 6,673,367; and 6,419,960; U.S. Publication Nos.

2003/0099711; 2006/0193877; 2007/0059270; 2007/01400983; 2007/0148239; US 2007/0264323; and 2009/0011027, the formulation disclosures of which are incorporated herein in their entirety.

[0059] In some embodiments, a physician is assisted in prescribing a dose of methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in an individual patient by a method comprising: determining the body weight of said individual patient; referring to a chart or reference tool that correlates a plurality of body weight ranges with a corresponding number of dosage amounts, each having a different level of methylphenidate; identifying a single dosage amount corresponding to a particular weight range in which said individual patient's weight falls in the chart or reference tool; and administering to said individual patient the identified dosage amount. The individual dosage amount can be based on the following chart:

Body Weight Range		Amount of Methylphenidate•HCl equivalent
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

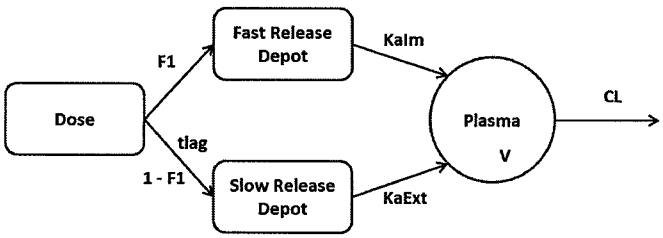
EXAMPLES

EXAMPLE 1

[0060] This example describes the development of a pharmacokinetic-pharmacodynamic model for the therapeutic effect of a particular methylphenidate formulation and its testing on a population of

pediatric patients with ADHD. The drug formulation tested in this example is designated MPH XR-ODT and described in U.S. Publication No. 2014/0030348, which is incorporated herein by reference.

[0061] The structural PK model for a plasma concentration following administration of the stimulant was described by two parallel inputs into a central compartment and linear elimination from the central compartment. This can be described graphically in the following manner:



[0062] The fast release depot represents the immediate release portion of the formulation that is readily absorbed into the plasma using a first-order rate constant (KaIm). The fraction of dose released from an immediate release coating was estimated with the relative bioavailability parameter (F1).

[0063] The slow release depot represents an extended release core that slowly releases drug following water permeation into the product core. The slow release was presumed to follow first-order absorption kinetics (KaExt). The time required for water to permeate a product core was represented with a lag time (tlag). The fraction of dose released from an extended release core was estimated as 1-F1.

[0064] First-order elimination from the central compartment appears to be adequately describe the elimination kinetics of the stimulant from the plasma. This elimination process was described with a volume of distribution (V) and clearance (CL).

[0065] Body weight appears as a covariate of CL and V which was included in the model in the following way:

$$CL_i = tvCL * Weight^{0.655} \quad \textbf{Equation 1}$$

$$V_i = tvV * Weight^{0.670} \quad \textbf{Equation 2}$$

where CL_i and V_i are the clearance and volume of distribution parameters for individual "i", tvCL and tvV are the typical population clearance and volume of distribution parameters, and weight is body weight in kg. Model parameters were determined using nonlinear mixed-effects modeling with first-order conditional maximum likelihood estimation using Phoenix NLME (Version 6.3).

[0066] The SKAMP total score data showed that over the 13 hour classroom evaluation, there appeared to be a gradual increase in the SKAMP total score over time. This phenomenon was readily obvious in the patients that were assigned to the placebo treatment arm. Therefore, the PD model required a drug effect component and a placebo effect component.

[0067] The basic PD model was described by the following equation:

$$E = BSL - DE + PE \quad \textbf{Equation 3}$$

where E is the observed SKAMP total score, BSL is the SKAMP total score just prior to dose administration under the classroom setting on Day 7 (Visit 8), DE is the reduction in SKAMP total score due to the presence of methylphenidate, and PE is the increase in SKAMP total score due to the placebo or classroom procedures.

[0068] The drug effect (DE) was modeled using an E_{max} equation as shown below:

$$DE = \frac{E_{max} * C_p}{EC_{50} + C_p} \quad \textbf{Equation 4}$$

where E_{max} is the maximum decrease in SKAMP total score, C_p is the plasma methylphenidate concentration, and EC_{50} is the concentration of methylphenidate required to elicit 50% of the maximal reduction in SKAMP total score. Using this model, the drug effect starts at zero when C_p is

zero. Increases in C_p create a linear increase in the drug effect while C_p is less than EC_{50}. Once C_p is greater than EC_{50}, the total drug effect asymptotically approaches the maximal response defined by E_{max}.

[0069] The placebo effect (PE) was modeled using a linear equation as shown below:

$$PE = Slope * t \qquad \textbf{Equation 5}$$

where Slope is the rate of change in SKAMP total score with time, and t is the time after dose administration. While a variety of models were evaluated, this linear model was adequate to fit the observed data from the patients assigned to the placebo treatment.

Thus the final structural PD model utilized in the analysis is shown below:

$$E = BSL - \left(\frac{E_{max} * C_p}{EC_{50} + C_p}\right) + (Slope * t) \qquad \textbf{Equation 6}$$

Linking PK and PD Structural Models

[0070] The PK and PD structural models were linked using a direct effect model. In a direct effect model, the effect directly correlated to the measured plasma concentrations of the drug. Plasma sampling for determination of methylphenidate concentrations was not performed, due to the potential impact of multiple venipunctures on the efficacy outcomes. The addition of plasma sampling procedures is expected to cause anxiety for the pediatric patients, and it would negatively affect the SKAMP Combined score. Because of the potential effect of blood sampling during a classroom evaluation, a modeling and simulation analysis was conducted in place of blood sampling in the pediatric patients. Therefore, the plasma methylphenidate concentration-time profile was simulated for each patient in the study using the previously described pediatric PK model, and the

final PK model parameter estimates. The simulated methylphenidate concentrations were then used to estimate the SKAMP Combined score using the PD structural model described above. As this was an integrated PKPD model, the simulation of plasma methylphenidate concentrations and the estimation of the PD parameters occurred during a single minimization procedure.

PK/PD Statistical Model

[0071] The PK/PD mixed-effects model has two components:

- A structural model that characterizes the effect-concentration-time relationship, and
- A random effects model containing between individual variability in the pharmacodynamic parameters, and a residual error component that accounts for within individual variability and measurement errors.

[0072] In the development of the random effects model, all parameters were assumed to be log-normally distributed and exponential between individual variability terms were included on the pharmacokinetic parameters found in the model. The form of the exponential error model is shown in Equation 7,

$$P_i = P * e^{\eta_i^P} \qquad \textbf{Equation 7}$$

where:

P_i = the true parameter value for individual i

P = the typical value (population mean) of the parameter

η_i^P = the difference between the true value for individual I and the typical value for the population, with a mean of 0 and a variance of ω^2

[0073] For the purpose of this analysis, additive (Equation 8) and proportional (Equation 9) residual error models were evaluated.

$$C_{ij} = \hat{C}_{ij} + \epsilon_{1ij} \qquad \textbf{Equation 8}$$

$$C_{ij} = \hat{C}_{ij} * (1 + \epsilon_{2ij}) \qquad \textbf{Equation 9}$$

where:

C_{ij} = the jth measured concentration for individual i

$\hat{C}_{ij}$ = the jth model predicted concentration for individual i

ε_{1ij} = the additive residual error for the jth concentration for individual I, and is normally distributed with a mean of 0 and a variance of ω_2^2.

E_{2ij} = the proportional residual error for the jth measurement for individual I, and is normally distributed with a mean of 0 and a variance of ω_1^2.

[0074] Hypothesis testing was performed using the likelihood-ratio test to discriminate among alternative hierarchical models. When comparing alternative models, the difference in the objective function is approximately chi-square distributed with *n* degrees of freedom, where *n* is the difference in the number of parameters between the hierarchical models. A decrease of 6.64 in the value of the objective function value (which is minus twice the maximum logarithm of the likelihood of the data) is significant under the likelihood-ratio test (n=1, $p<0.01$). A decrease of 10.83 in the value of the objective function value is significant under the likelihood-ratio test (n=1, $p<0.001$). Goodness of fit was evaluated using diagnostic scatter plots. No covariates were evaluated in this analysis.

RESULTS

[0075] The final analysis dataset for the PKPD model contained 640 SKAMP total score measurements from 81 pediatric patients. There were 53 (65.4%) male patients in the analysis dataset, and 42 (51.9%) patients received the formulation and the remaining 39 (48.1%) patients received placebo during the Day 7 classroom evaluation. The distribution of patients across the formulation dose range is shown in Table 1.

[0076] Table 1: Number of Patients at Each Dose Level and Treatment

	Number of Patients on Day 7 (Visit 8)	
Optimal Dose Level (mg/day)	**Active Treatment**	**Placebo Treatment**
20 mg/day	6	4
30 mg/day	12	8
40 mg/day	11	12
60 mg/day	13	15
Total	**42**	**39**

PKPD Model - Base Model

[0077] The integrated PKPD model with the PK and PD structural models was fit to the SKAMP total score measurements. The base PKPD model consists of 4 structural parameters, 3 between individual variability parameters, and a residual error parameter. These parameters are described below, respectively:

- Slope represents the change in SKAMP total score per hour during the 13-hour classroom session
- E0 represents the SKAMP total score at time = 0, just prior to dose administration (which is also 24 hours after administration of the previous dose)
- EC50 is the concentration of methylphenidate required to achieve 50% of the maximal reduction in SKAMP total score
- Emax is the maximum reduction in SKAMP total score with administration of methylphenidate
- Between individual variability parameters were included on E0, EC50 and Slope
- Residual error was modeled using an additive error parameter

[0078] A placebo model was included after reviewing the mean Change from Baseline in SKAMP total score for patients in the placebo treatment arm (Figure 1). Over the 13-hour classroom session, the SKAMP score tended to increase in the absence of any treatment intervention. The reason for

this increase is not known; however, it is critical to include this change in response in the PKPD model to accurately depict changes in SKAMP total score.

[0079] See Figure 1: Mean (±SE) Change from Baseline SKAMP Total Score for Patients Assigned to the Placebo Treatment (n = 39)

[0080] Linear, polynomial, and Emax models were fit to the placebo treatment data. The linear model provided the best overall fit and fewest parameters, therefore the linear placebo model was included in the base PKPD model. Final parameters and variability estimates for the base PKPD model are shown in Table 2.

Table 2: Base PKPD model parameter estimates

Structural model parameters	**Estimate (%CV)**
Slope (1/h)	0.691 (12.1%)
E0	21.9 (5.0%)
EC50 (ng/mL)	14.24 (28.7%)
Emax	38.1 (12.5%)
Between individual variability parameters	**Estimate (%Shrinkage)**
ωSlope	0.365 (30.6%)
ωE0	0.154 (8.0%)

ωEC50	0.157 (63.0%)
Residual variability parameter	**Estimate (%CV)**
ε (additive)	5.70 (3.5%)

%CV = percentage coefficient of variation calculated as standard deviation/estimate * 100
%Shrinkage = percentage shrinkage to mean parameter estimate calculated as 1- standard deviation/estimate*100

[0081] All structural model parameters except EC_{50} were estimated with good precision, as shown by the percentage coefficient of variation of 12.5% or less. The percentage coefficient of variation or EC_{50} was 28.7%. The between individual variability parameter for E0 was small, but the between individual variability parameter for Slope and EC50 were large (shrinkage of 30.6% and 63.0%, respectively). Residual variability (5.70) was moderately large relative to baseline SKAMP scores (21.9).

[0082] The diagnostic plots showed a good fit of the base PKPD model to the SKAMP total score observations. Residuals were uniformly distributed with time and methylphenidate concentrations with no obvious bias.

PKPD Model - Covariate Model

[0083] Individual values for the covariates BMI, sex, weight, age, race and ethnicity were explored graphically by plotting the covariates on the x-axis and the ETA (η_i^P) for each pharmacodynamic parameter. The ETA represents the difference between the individual PD response estimate and the typical value for the entire population. Relationships between the covariate and ETA suggest that the variations in individual parameter estimates may be explained by differences in the covariates between subjects. Two potential covariates emerged from the graphical exploration: Age as a covariate for E0 and weight as a covariate for E0. In pediatric patients, age and weight are collinear

because weight tends to increase with age. Both covariates (age and weight) were added to the base PKPD model, and both resulted in statistically significant reductions in the objective function value, with weight being a more significant covariate. In both models, subjects with higher weights or ages tended to have lower baseline SKAMP total scores. Other parameters (EC50, Emax, Slope and residual error) were unchanged.

[0084] The objective of this analysis is to model the effect of methylphenidate on the SKAMP total score. While the finding that baseline SKAMP total scores are lower in older and heavier pediatric patients is statistically significant, the inclusion of a covariate on a baseline parameter does not provide additional information about the effects of methylphenidate. Therefore, these covariates were not included, and the Base PKPD model was considered the Final PKPD model.

Posterior Predictive Check of Final PKPD Model

[0085] A posterior predictive check was performed on the final PKPD model. The posterior predictive check suggests that the final PKPD model can accurately predict the SKAMP total score over the 13-hour classroom test period.

Simulations

[0086] The final PKPD model was used to perform simulations of SKAMP total scores in pediatric patients. At each dose strength, 500 separate simulated profiles were produced across the weight range 15 – 80 kg. Simulated SKAMP total score data was divided by dose level and body weight as shown in Table 3:

Table 3: MPH XR-ODT Dose Levels and Patient Body Weight Groups

MPH XR-ODT Dose Levels	Patient Body Weight Groups[i)]
10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg	5 kg, 10 kg, 15 kg, 20 kg, 25 kg, 30 kg, 35 kg, 40 kg, 45 kg, 50 kg, 55 kg, 60 kg, 65 kg, 70 kg, 75 kg, 80 kg, 85 kg, 90 kg, 95 kg

[i)] Body weight groups are defined by the median of the range of body weights. For example, the 20 kg group includes individuals between 17.5 kg and <22.5 kg, and the 25 kg group includes individuals between 22.5 and <27.5 kg.

[0087] The mean SKAMP total score profiles for each MPH XR-ODT dose level was plotted by body weight. As expected, MPH XR-ODT dose levels ≥40 mg provide the greatest reduction in SKAMP total score for nearly all body weights. Interestingly, at body weights ≤45 kg, there is little differentiation between the response at the 40 – 60 mg dose levels. Beginning at 45 kg, a separation is observed with the 10 mg and 20 mg dose levels providing little to no reduction in SKAMP total score, while significant reductions are observed with the 40-60 mg dose levels. Thus, the shape of the dose-response curve varies as body weight changes.

[0088] For each simulated SKAMP total score profile, the maximum decrease from baseline SKAMP total score was calculated and those maximum changes were summarized by dose level and body weight. From this data, it is clear that greater reductions in SKAMP total scores are observed with higher doses at a constant body weight (i.e., lines slope downward from left to right). Similarly, for a given dose strength, pediatric patients with lighter body weight experience a greater reduction in SKAMP total score than heavier patients at the same dose level (i.e., line for 15 kg body weight is below line for 80 kg body weight).

[0089] The mean baseline SKAMP total score was approximately 22 (E0 estimate of 21.99, Table 2). Therefore a decrease of 20 points in the SKAMP total score would represent a near complete reversal of the symptoms for the average patient, as measured by SKAMP. The data in Table 4 clearly show that patients who are heavier generally require a larger MPH XR-ODT dose. In addition, the beneficial effects of methylphenidate appear to plateau at higher doses in subjects such

that increasing the MPH XR-ODT dose may not provide increased symptom control in some patients.

Table 4: Percent of Simulation Patients with a SKAMP Total Score Decrease >20

	Percent of Simulated Patients by MPH XR-ODT Dose Level					
Weight Group	**10 mg**	**20 mg**	**30 mg**	**40 mg**	**50 mg**	**60 mg**
5 kg	**53.3**	**70.0**	**88.2**	**100.0**	**88.9**	**100.0**
10 kg	37.8	**75.0**	**83.3**	**100.0**	**96.4**	**97.1**
15 kg	23.8	**58.6**	**86.4**	**96.6**	**96.2**	**97.0**
20 kg	15.8	**64.0**	**69.7**	**83.3**	**75.0**	**92.9**
25 kg	7.4	23.5	**70.0**	**72.4**	**77.8**	**88.0**
30 kg	8.0	48.6	**57.7**	**75.9**	**80.0**	**88.9**
35 kg	15.8	30.4	**59.3**	**51.9**	**66.7**	**95.5**
40 kg	25.9	23.8	40.5	**55.6**	**74.1**	**84.4**
45 kg	15.4	28.6	**52.2**	**68.2**	**55.0**	**69.0**
50 kg		20.8	17.2	**53.3**	**76.0**	**70.8**
55 kg	12.1	20.7	36.0	**50.0**	**55.2**	**93.1**
60 kg	7.7	20.0	44.0	47.6	**60.0**	**76.9**
65 kg	6.3	18.2	25.0	48.4	**50.0**	**58.3**
70 kg		4.2	34.5	**50.0**	**53.1**	**64.3**
75 kg	11.1	22.6	30.4	42.9	**66.7**	38.5
80 kg		20.0	26.1	39.3	**60.0**	**73.1**
85 kg	3.6	6.7	29.2	34.8	44.4	**64.7**
90 kg	9.4	9.1	15.8	26.9	**53.6**	**59.1**
95 kg	9.1	4.0	35.3	36.4	**60.0**	**63.0**

Note: Values ≥50% are in boldface font.

[0090] Assuming that the target MPH XR-ODT dose should provide a SKAMP Combined score reduction >20 in at least 50% of subjects, the optimal MPH XR-ODT doses by body weight can be determined. A linear regression of those optimal doses versus body weight from the simulations was performed. The optimal doses for a range of body weights from 7–100 kg is presented in Table 5.

Table 5: Optimal MPH XR-ODT Dose by Body Weight

Body Weight Range		Amount of Methylphenidate•HCl equivalent
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

CLAIMS

1. A method of treating attention deficit hyperactivity disorder (ADHD) in an individual patient comprising administering to said individual patient a therapeutically effective amount for said patient of an oral dose form containing an ADHD-effective agent,

wherein the oral dose form has an *in vitro* release profile of: 30-33% of the ADHD-effective agent is released within the first 30 minutes after the oral dose form is introduced into an *in vitro* dissolution assay, 34-42% of the agent is released within 2 hours, 40-80% of the agent is released within 4 hours, and 80-100% of the agent is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

.

2. Use of an attention deficit hyperactivity disorder (ADHD)-effective agent in the manufacture of a medicament for treating ADHD in an individual patient,

wherein the medicament is provided in an oral dose form that has an *in vitro* release profile of: 30-33% of the ADHD-effective agent is released within the first 30 minutes after the oral dose form is introduced into an *in vitro* dissolution assay, 34-42% of the agent is released within 2 hours, 40-80% of the agent is released within 4 hours, and 80-100% of the agent is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg

Body Weight Range		Amount of Methylphenidate•HCl equivalent
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

.

3. A method of treating attention deficit hyperactivity disorder (ADHD) comprising administering to an individual patient a therapeutically effective amount for said individual patient of an oral dose form containing an ADHD-effective agent, wherein, for *in vivo* pharmacokinetic parameters of the composition, at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ has a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		Amount of Methylphenidate•HCl equivalent
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

.

4. Use of an attention deficit hyperactivity disorder (ADHD)-effective agent in the manufacture of a medicament for treating ADHD in an individual patient,

wherein the medicament is provided in an oral dose form,

wherein for *in vivo* pharmacokinetic parameters of the medicament, at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ has a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition,

wherein the ADHD-effective agent comprises methylphenidate, and

wherein the therapeutically effective amount of the oral dose form is correlated to the body weight of said individual patient as follows:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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5. The method of claim 1 or 3 or the use of claim 2 or 4, wherein the oral dose form comprises a first plurality of drug-resin particles that are coated with a delayed release coating and a second plurality of drug-resin particles that are not coated with a delayed release coating.

6. The method of claim 1 or 3 or the use of claim 2 or 4, wherein the oral dose form comprises a multitude of multicoated particles made of two populations of drug layered beads of IR (immediate release) and ER (extended release) beads.

7. The method of claim 1 or 3 or the use of claim 2 or 4, wherein the oral dose form comprises (1) an immediate release methylphenidate component and (2) a sustained release methylphenidate component.

8. The method or the use of claim 7, wherein the sustained release component comprises a water-insoluble, water-permeable, pH-independent, barrier coated methylphenidate-ion exchange resin complex.

9. The method of claim 1 or 3 or the use of claim 2 or 4, wherein the oral dose form comprises (a) a sustained release racemic methylphenidate component comprising a water-insoluble, water-permeable, pH-independent barrier coated, racemic methylphenidate-ion exchange resin complex in a polymeric matrix, wherein said barrier coating is over the racemic methylphenidate-ion exchange resin complex-matrix; (b) a first immediate release component which comprises an immediate release uncoated racemic methylphenidate-ion exchange resin complex; and (c) a second immediate release racemic methylphenidate component which comprises an uncomplexed racemic methylphenidate.

10. The method of claim 3, wherein the oral dose form comprises a first component comprising a first population of ADHD-effective agent particles and at least one subsequent component, each subsequent component comprising a subsequent population of active ingredient-containing particles, the ADHD-effective agent contained in the first and subsequent components being the same or different, wherein the at least one subsequent population of ADHD-effective agent particles further comprises a modified release coating or, alternatively or additionally, a modified release matrix material, such that the composition following oral delivery to a subject delivers the ADHD-effective agent in a pulsatile manner, or the use of claim 4, wherein the medicament comprises a first component comprising a first population of ADHD-

effective agent particles and at least one subsequent component, each subsequent component comprising a subsequent population of active ingredient-containing particles, the ADHD-effective agent contained in the first and subsequent components being the same or different, wherein the at least one subsequent population of ADHD-effective agent particles further comprises a modified release coating or, alternatively or additionally, a modified release matrix material, such that the medicament following oral delivery to a subject delivers the ADHD-effective agent in a pulsatile manner.

11. A method of assisting a physician in prescribing a dose of methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in an individual patient, comprising:

a. determining the body weight of said individual patient;

b. referring to a chart or reference tool that correlates a plurality of body weight ranges with a corresponding number of dosage amounts each having a different level of methylphenidate; and

c. identifying a single dosage amount corresponding to a particular weight range in which said individual patient's weight falls in the chart or reference tool,

wherein the chart or reference tool includes the following correlations between body weight range and said dosage amount of methylphenidate hydrochloride equivalent:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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wherein the methylphenidate is formulated in a composition having an *in vitro* release profile of: 30-33% of the methylphenidate is released within the first 30 minutes after the oral dose form is introduced into an *in vitro* dissolution assay, 34-42% of the methylphenidate is released within 2 hours, 40-80% of the methylphenidate is released within 4 hours, and 80-100% of the methylphenidate is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2, and/or

wherein the methylphenidate is formulated in a composition that produces an *in vivo* release profile having at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ having a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition.

12. A method of treating attention deficit hyperactivity disorder (ADHD) in an individual patient, comprising:

a. determining the body weight of said individual patient;

b. referring to a chart or reference tool that correlates a plurality of body weight ranges with a corresponding number of dosage amounts each having a different level of methylphenidate;

c. identifying a single dosage amount corresponding to a particular weight range in which said individual patient's weight falls in the chart or reference tool; and

d. administering to said individual patient the identified dosage amount,

wherein the chart or reference tool includes the following correlations between body weight range and said dosage amount of methylphenidate hydrochloride equivalent:

Body Weight Range		**Amount of Methylphenidate•HCl equivalent**
< 12 kg	< 26 lb	10 mg
12 – 33 kg	26 – 73 lb	20 mg
33 – 55 kg	73 – 121 lb	30 mg
55 – 77 kg	121 – 169 lb	40 mg
77 – 99 kg	169 – 218 lb	50 mg
> 99 kg	> 218 lb	60 mg

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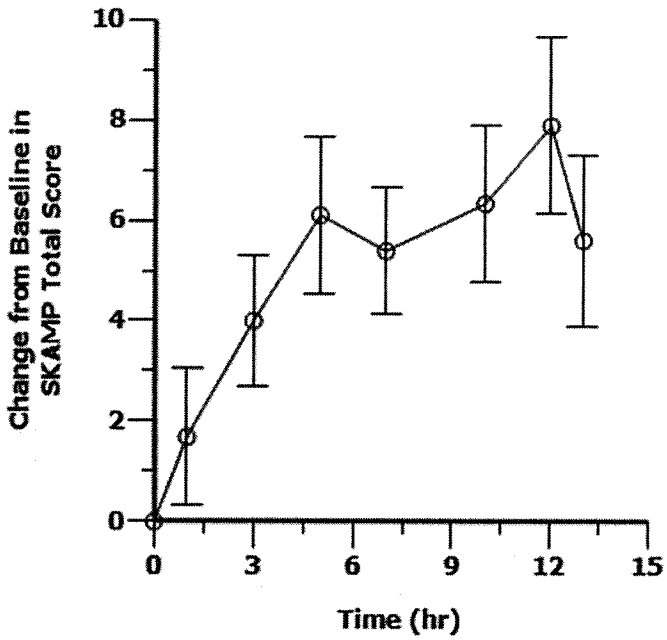
wherein the methylphenidate is formulated in a composition having an *in vitro* release profile of: 30-33% of the methylphenidate is released within the first 30 minutes after the oral dose form is introduced into an *in vitro* dissolution assay, 34-42% of the methylphenidate is released within 2 hours, 40-80% of the methylphenidate is released within 4 hours, and 80-100% of the methylphenidate is released within 24 hours, wherein the conditions of the dissolution assay are an initial dissolution medium of 0.1 N HCl, and after 2 hours, the medium is adjusted to a pH of about 6.8; and the dissolution assay is performed using a USP Apparatus 2, and/or

wherein the methylphenidate is formulated in a composition that produces an *in vivo* release profile having at least one *in vivo* pharmacokinetic parameter selected from the group consisting of C_{max}, AUC_{0-5}, AUC_{5-12}, AUC_{5-24}, AUC_{5-t}, AUC_{0-12}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$ having a 90% confidence interval with upper and lower bounds within a range from 80%-125% of the value of the same parameter(s) for a bioequivalent reference composition.


Change from Baseline in SKAMP Total Score
10
8
6
4
2
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Time (hr)

Figure 1