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(54) **Title**: MODIFIED RELEASE PHARMACEUTICAL COMPOSITIONS OF METHYLPHENIDATE OR SALTS THEREOF

(57) **Abstract**: The present invention relates to modified release pharmaceutical compositions of methylphenidate or salts thereof. In particular, the present invention relates to modified release pharmaceutical compositions comprising at least one immediate release and at least one extended release component of methylphenidate or salts thereof. The composition may provide extended and specific release of methylphenidate or salts thereof to achieve therapeutically effective plasma concentration over a period of 12 hours to treat attention deficit disorders when administered to a patient in need thereof. The invention also includes process of preparing such composition.

# MODIFIED RELEASE PHARMACEUTICAL COMPOSITIONS OF METHYLPHENIDATE OR SALTS THEREOF

## Field of the Invention

The present invention relates to modified release pharmaceutical compositions of methylphenidate or salts thereof. In particular, the present invention relates to a modified release pharmaceutical compositions comprising at least one immediate release and at least one extended release component of methylphenidate or salts thereof. The composition may provide extended and specific release of methylphenidate or salts thereof to achieve therapeutically effective plasma concentration over a period of 12 hours to treat attention deficit disorders when administered to a patient in need thereof. The invention also includes process of preparing such composition.

## Background of the Invention

Methylphenidate Hydrochloride, a scheduled II controlled substance, is currently marketed as a mild central nervous system (CNS) stimulant and the drug of choice for treatment of Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) in children.

The drug is well absorbed throughout the gastrointestinal tract. However, it has an extremely short half-life, which necessitates a multi-dose treatment regimen for conventional (immediate release) dosage forms such as currently available 5, 10, and 20 mg tablets. Due to high $C_{max}$, oral administration of 10 and 20 mg Ritalin® is reported to result in notable side effects such as anorexia, weight loss, dizziness, etc.

Furthermore, it requires the hyperactive children to be dosed in school thus causing hardship to school authorities as well as parents. The drawback of methylphenidate is that it also produces a euphoric effect when administered intravenously or through inhalation, thus presenting a high potential for substance abuse.

Sustained release formulations for once-a-day dosing, such as 20 mg Ritalin® tablets currently available from Novartis and Geneva (generic version), were developed with the objective of providing efficacy for 8 hours, thereby improving compliance and reducing the incidence of diversion. However, there are reports which strongly suggest that the sustained release formulations exhibit a slower onset of action/efficacy compared to the immediate release dosage forms.

Osmotic drug delivery based one-a day oral formulation of methylphenidate HCl is also available. The dosage form contains a drug overcoat that is designed to deliver a portion of the dose for rapid onset of action and deliver the remainder of the dose in a controlled manner for about 10 hours.

U.S. Patent No. 5,908,850 discloses a sustained release dosage form containing d-threo-methylphenidate (commonly known as dexmethylphenidate) or pharmaceutically acceptable salts thereof thus minimizing hyperactivity and side effects.

U.S. Patent No. 6,344,215 discloses a modified release dosage methylphenidate capsule comprising immediate and extended release beads, each prepared by layering over the core particles.

The formulations of methylphenidate know in the art are complicated dosage forms. Manufacturing cost of such dosage forms is expected to be very high and hence resulting in a high cost of treatment. Thus, there exist a dire need to develop modified release dosage forms of methylphenidate with moderate cost of goods and having not only a rapid onset of action but also with a significantly longer duration of action.

The present inventors have surprisingly found that it is possible to achieve therapeutically efficacious plasma concentrations with rapid onset of action and maintained it over a 12-hour period, thus eliminating the need to dose children in the school. These objectives can be achieved by devising a new modified release

composition of methylphenidate containing both immediate and extended release components of methylphenidate, such that immediate release component of the composition is not in the form of core particles coated with layer of methylphenidate. The composition is simple and economical to manufacture and also involve less number of manufacturing steps.

## Summary of the Invention

In one general aspect, there is provided a modified release pharmaceutical composition comprising at least one immediate release and at least one extended release component comprising methylphenidate or salts thereof, wherein the extended release component is not in the form of core particles coated with layer of methylphenidate.

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In one general aspect, there is provided a modified release pharmaceutical composition comprising at least one immediate release and at least one extended release component comprising methylphenidate or salts thereof, wherein the immediate release component and the extended release component is not in the form of core particles coated with layer of methylphenidate.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of a mixture of methylphenidate and one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of a mixture of methylphenidate and one or more pharmaceutically acceptable excipients and the extended release component comprises core particles coated with one or more layers of methylphenidate, which is further coated with one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of mixture of methylphenidate and one or more pharmaceutically acceptable excipients and the extended release component comprises matrix of methylphenidate, and one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of granules comprising methylphenidate or salts thereof and one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salt thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of granules comprising methylphenidate and one or more pharmaceutically acceptable excipients and the extended release component comprises core particles coated with one or more layers of methylphenidate, which is further coated with one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of granules comprising methylphenidate and one or more pharmaceutically acceptable excipients and the extended release component comprises matrix of methylphenidate, and one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of one or more mini-tablets.

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In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of one or more mini-tablets comprising methylphenidate and one or more pharmaceutically acceptable excipients and the extended release component comprises matrix of methylphenidate, and one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate

release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of extrudates comprising methylphenidate or salts thereof and one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salt thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of extrudates and the extended release component comprises core particles coated with one or more layers of methylphenidate, which is further coated with one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release component is in the form of extrudates comprising methylphenidate and one or more pharmaceutically acceptable excipients and the extended release component comprises matrix of methylphenidate, and one or more rate controlling substances.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein both the immediate release and extended release components are in the form of extrudates comprising methylphenidate and one or more pharmaceutically acceptable excipients.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, wherein the immediate release and extended release components of the composition are in

the form of tablets, mini-tablets, granules, pellets, spheroids, beads, or mixtures thereof.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, characterized in that the composition retains at least 90% w/w of the potency of methylphenidate or salts thereof when stored at $40^0$C and 60% relative humidity for 3 months.

In another general aspect, there is provided a modified release pharmaceutical composition of methylphenidate or salts thereof comprising at least one immediate release and at least one extended release component of methylphenidate, characterized in that the composition is bioequivalent to the formulation of methylphenidate marketed under the trade name Metadate CD®.

In another general aspect, the immediate release granules as disclosed in the present invention can be prepared by wet granulation, dry granulation or slugging.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;
(b) granulating the mixture prepared in step (a) to form immediate release component in the form of granules;
(c) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;
(d) granulating the mixture prepared in step (c) to form matrix type extended release component;
(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form immediate release component in the form of a dry blend;
(b) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(c) optionally, coating a barrier layer over the methylphenidate layered particles;
(d) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component;
(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and granulating with a vehicle to form granules as an immediate release component
(b) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(c) optionally, coating a barrier layer over the methylphenidate layered particles;
(d) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component;
(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;

(b) granulating the mixture prepared in step (a) followed by compression to form immediate release component in the form of mini-tablets;
(c) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(d) optionally, coating a barrier layer over the methylphenidate layered particles;
(e) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component; and
(f) filling the immediate release component prepared in step (b) and the extended release component prepared in step (e) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and one or more vehicles to obtain a plastically deformable mass;
or processing methylphenidate or salts thereof along with one or more polymer to form a molten mass;
(b) extruding the mixture or molten mass obtained in step (a) to obtain cylindrical extrudates having desired length and diameter to form immediate release components in the form of extrudates;
(c) optionally, spheronizing the extrudates to form immediate release components in the form of spherical pellets;
(d) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(e) optionally, coating a barrier layer over the methylphenidate layered particles;
(f) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component; and
(g) filling the immediate release component prepared in step (b) or (c) and extended release component prepared in step (f) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;

(b) granulating the mixture prepared in step (a) followed by compression to form immediate release component in the form of mini-tablets;

(c) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;

(d) granulating the mixture prepared in step (c) to form matrix type extended release component;

(e) filling the immediate release component prepared in step (b) and the extended release component prepared in step (d) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and one or more vehicles to obtain a plastically deformable mass;

or processing methylphenidate or salts thereof along with one or more polymer to form a molten mass;

(b) extruding the mixture or molten mass obtained in step (a) to obtain cylindrical extrudates having desired length and diameter to form immediate release components in the form of extrudates;

(c) optionally, spheronizing the extrudates to form immediate release components in the form of spherical pellets;

(d) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;

or processing methylphenidate or salts thereof along with one or more rate controlling substances to form a molten mass;

(e) granulating the mixture prepared in step (d) to form matrix type extended release components;

or extruding the molten mass obtained in step (d) to obtain extended release components in the form of cylindrical extrudates having desired length and diameter;
(f) optionally spheronizing the extrudates prepared in step (e) to form extended release components in the form of pellets
(g) filling the immediate release components prepared in step (b) or (c) and the extended release components prepared in step (e) or (f) in a capsule.

In another general aspect, there is provided a method of treating ADD or ADHD by administering the patient in need thereof the modified release pharmaceutical composition of methylphenidate or salts thereof as substantially described throughout the specification.

## Detailed Description of the Invention

The present invention relates to a novel modified release composition comprising one or more immediate release components and one or more extended release components of methylphenidate or salts thereof, wherein the immediate release and/or the extended release components are not in the form of core particles coated with layer of methylphenidate.

In particular, the immediate release components are present in the form of methylphenidate and excipient admixture, granules, mini-tablets, extrudates or mixtures thereof and the extended release components are present in the form of core particles coated with one or more layers of methylphenidate, which is further coated with one or more rate controlling substances, matrix of methylphenidate and one or more rate controlling substances, or extrudates comprising methylphenidate and one or more pharmaceutically acceptable excipients or mixtures thereof.

Preferably, the immediate release component in the composition of the present invention is in the form of mixture of methylphenidate or salts thereof and one or more pharmaceutically acceptable excipients, granules, mini-tablet or extrudates comprising methylphenidate or salts thereof and one or more pharmaceutically

acceptable excipients and the extended release component comprises matrix of methylphenidate or salts thereof and one or more release controlling substances. Such compositions may provide rapid onset of action as well as a significantly longer duration of action. The composition also involves simple and economical manufacturing process.

In one embodiment, the modified release pharmaceutical composition comprises of at least one immediate release and at least one extended release components comprising methylphenidate or salts thereof, wherein the immediate release component and/or the extended release component is not in the form of core particles coated with layer of methylphenidate.

In another embodiment, the modified release composition of the present invention is bioequivalent to formulation of methylphenidate marketed under the trade name Metadate CD®.

In another embodiment, the modified release unit dosage form of the present invention retains at least 90% w/w of the potency of methylphenidate or salts thereof when stored at 25°C and 40% relative humidity or at $40^0$C and 25% relative humidity for 3 months.

In another embodiment, the modified release unit dosage form of the present invention is characterized in that it provides therapeutically effective plasma concentration of methylphenidate or salts thereof over a period of 12 hours.

The granules as disclosed in the present invention can be prepared by the methods known to those skilled in the art such as wet granulation, dry granulation or slugging.

The term “component” used throughout the specification refers to dry blend or mixture (e.g. powder), mini-tablet, tablet, pellet, bead or granule prepared by standard methods known to the person skilled in the art, including but not limited to compression, granulation, spray coating, and extrusion/spheronization.

The term “methylphenidate” used throughout the specification refers to not only methylphenidate per se, but also its other pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof.

The term "modified release" used throughout the specification shall apply to dosage forms, matrices, particles, coatings, portions thereof, or compositions that alter the release of an active ingredient in any manner. Types of modified release include controlled, prolonged, sustained, extended, delayed, and the likes.

The term “matrix” used throughout the specification refers to the dispersion of drug within one or more release modifying substances and optionally one or more pharmaceutical excipients, or mixture thereof.

The term “plastically deformable mass” used throughout the specification refers to the mass capable of passing through extruder or perforated mesh.

The term “extrudates” used throughout the specification refers to a type of physical form (e.g. particles, pellets, beads) obtained by extruding the plastically deformable (moistened or molten) mass through extruder or perforated mesh. A typical method of preparing the extrudates involves a step of heating a mixture of drug along with suitable vehicle (e.g. water) under mechanical pressure in a cooker extruder. An alternate method is extruding the molten mixture of drug-polymer through an extruder.

In a preferred embodiment, the immediate release component of the present invention is in the form of granules comprising methylphenidate and one or more pharmaceutically acceptable excipients.

In another preferred embodiment, the immediate release component of the present invention is in the form of a blend of methylphenidate and one or more pharmaceutically acceptable excipients.

In another preferred embodiment, the immediate release component of the present invention is in the form of one or more mini-tablets comprising of methylphenidate or salts thereof and one or more pharmaceutically acceptable excipients.

In another embodiment, the immediate release component comprises plurality of cores prepared by processing, particularly compressing the pharmaceutically acceptable excipients to form mini-tablets comprising methylphenidate or salts thereof.

In yet another preferred embodiment, the immediate release component of the present invention is in the form of mini-tablets of methylphenidate and one or more pharmaceutically acceptable excipients.

Polymers suitable for preparing extrudates of the present invention include, but not limited to, one or more water-soluble, water-insoluble or water-swellable thermoplastic polymers.

The water soluble polymers that can be used, according to the present invention, comprises of homopolymers and co-polymers of N-vinyl lactams, especially homopolymers and co-polymers of N-vinyl pyrrolidone, e.g., polyvinylpyrrolidone (PVP), co-polymers of PVP and vinyl acetate, co-polymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate, dextrins such as grades of maltodextrin, cellulose esters and cellulose ethers, high molecular polyalkylene oxides, such as polyethylene oxide and polypropylene oxide, and co-polymers of ethylene oxide and propylene oxide. The water soluble polymer is preferably present in the range wherein the ratio of drug to polymer is 1:0.5 to 1:6.

The water insoluble polymers that can be used, according to the present invention, comprises of acrylic copolymers, e.g., Eudragit E100 or Eudragit EPO; Eudragit L30D-55, Eudragit FS30D, Eudragit RL30D, Eudragit RS30D, Eudragit NE30D, Acryl-Eze (Colorcon Co.); polyvinylacetate, for example, Kollicoat SR 30D (BASF Co.); cellulose derivatives such as ethylcellulose, cellulose acetate, e.g., Surelease (Colorcon Co.), Aquacoat ECD and Aquacoat CPD (FMC Co.). The most preferred water insoluble polymer is Eudragit E100. The water insoluble polymer is preferably present in the range wherein the ratio of drug to polymer is 1:1 to 1:6. Additionally, the water insoluble polymer may be combined with organic acids, such as from citric acid, tartaric acid, glycolic acid, etc.

The extrudates as disclosed in the present invention can also be prepared by various other methods known to those skilled in the art such as extrusion.

In an embodiment, the extended release components are in the form of beads.
The beads may be matrix type or of inert core coated with one or more drug layers and optionally coated with one or more barrier coating.

In a further embodiment, the extended release component of the present invention may be comprised of an inert particle such as a commercially available non-pareil sugar sphere. Methylphenidate is layered on the sugar spheres from an aqueous solution of the drug and a binder such as polyvinylpyrrolidone (PVP). The drug layered beads are provided with up to 4%, preferably up to 2% w/w barrier coat using a film-former, such as hydroxypropylmethylcellulose (HPMC) (e.g., Opadry Clear).

Extended release components can be prepared by coating drug coated/barrier coated beads as mentioned above with a solution or an aqueous dispersion of a dissolution rate controlling polymer thereby forming an extended release membrane coating on the IR bead.

The release controlling substances which can be used may be selected from the group consisting of hydrophilic agents (e.g. water-soluble polymers), lipophilic agents

(water-insoluble polymers) and inert matrix agents, wherein the hydrophilic agents are selected from the group of pharmaceutical excipients which generate a gel in contact with water, including cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose and the like; noncellulose polysaccharides such as galactomannanes, guar gum, carob gum, gum arabicum, alginates, pectins, and the like; polyvinylpyrrolidone; polyvinylacetate polymers and copolymers; acrylic acid polymers and copolymers, polyethylene oxide and mixtures thereof; the lipophilic agents are selected from the group consisting of waxes such as white wax, bees wax, carnauba wax and the like; fatty acids and alcohols such as stearic acid, palmitic acid, lauric acid and the like, and cetyl alcohol, cetostearyl alcohol, stearyl alcohol and the like; fatty acids esters such as monostearates of propylene glycol and fatty acid esters of sucrose, sucrose distearate and the like; and glycerides such as mono-, di- or triglycerides, e.g. palmitin, stearin, behenic, laurin, myristin, hydrogenated vegetable, castor, cottonseed oils, glyceril behenate and the like; ethyl cellulose; acrylic acid polymers and copolymers (available commercially under Eudragit® brand); and mixtures thereof; and the inert agents are selected from the group consisting of thermoplastic polymers, which are insoluble and indigestible in the gastrointestinal fluids, such as polyvinyl chloride, polyethylene, vinyl acetate/vinyl chloride copolymers, polymethylmethacrylates, polyamides, silicones, ethyl cellulose, polystyrene, and mixtures thereof.

Preferred examples of rate controlling substances include, but are not limited to, ethylcellulose (e.g., Aquacoat® ECD-30), neutral copolymers based on ethylacrylate and methylmethacrylate, and copolymers of acrylic and methacrylic acid esters having quaternary ammonium groups. The membrane coated beads are also typically seal coated with HPMC to produce extended release beads.

In an embodiment, the immediate and/or extended release component in accordance with the invention are provided with up to 4%, preferably up to 2% w/w barrier coat using a film-former, such as hydroxypropylmethylcellulose (HPMC) (e.g., Opadry Clear).

The immediate release and extended release components are filled into hard gelatin capsules at predetermined ratios to produce modified release capsule. Ratios of immediate release and extended release components found to provide desirable release profiles ranges from about 10:90 to 50:50, preferably from 20:80 to 40:60, and most preferably at a ratio of 30:70.

The amount of methylphenidate in the composition can be varied widely. A typical dose is expected to be from about 10 to 60 mg of methylphenidate. Immediate release components typically will account for about 20 to 40% of the dose. The methylphenidate content in the extended release components may range from 5 to 20% w/w. Those skilled in the art will be able to select an appropriate amount of methylphenidate for extended release component to achieve the desired dosage. Generally, the rate controlling substance in the methylphenidate extended release component may vary from 5 to 25%, preferably from 5 to 20% and more preferably from 5 to 10% by weight based on the total weight of the extended release component, depending on the rate controlling substance and pharmaceutical excipients selected.

The thickness of the membrane layer or the amount or type of rate controlling substance selected depends on the desired release profile, and is optimized for achieving a desired in vitro release profile, which is predicted based on the in vitro/in vivo correlations and efficacy study results. Preferably, the release profile provides an immediate bolus of drug and extended release of the drug at a relatively constant rate for an extended period of time (over 12 hours or more).

The composition according to the present invention may comprise extended release component, preferably in the form of pellets, which provides only an extended release profile and granules comprising methylphenidate with one or more pharmaceutical excipients exhibiting immediate release.

The composition according to the present invention may comprise one bead population, which provides only an extended release profile and a blend of methylphenidate with one or more pharmaceutical excipients exhibiting immediate release.

The modified release composition of the present invention can be prepared by methods known to the person skilled in the art.

In an embodiment, the process of manufacturing a modified release methylphenidate composition comprises the steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;
(b) granulating the mixture prepared in step (a) to form immediate release component in the form of granules;
(c) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;
(d) granulating the mixture prepared in step (c) to form extended release component;
(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

The modified release composition of the present invention can be prepared by methods known to the person skilled in the art.
In an embodiment, the process of manufacturing a modified release methylphenidate composition comprises the steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form immediate release component in the form of a dry blend;
(b) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(c) coating a barrier layer over the methylphenidate layered particles;

(d) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component;
(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (a) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and granulating with a vehicle to form granules as an immediate release component
(b) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(c) optionally, coating a barrier layer over the methylphenidate layered particles;
(d) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component;
(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

In an embodiment, the process for preparation of a modified release capsule comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;
(b) granulating the mixture prepared in step (a) followed by compression to form immediate release component in the form of mini-tablets;
(c) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(d) optionally, coating a barrier layer over the methylphenidate layered particles;
(e) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component; and

(f) filling the immediate release component prepared in step (b) and the extended release component prepared in step (e) in a capsule.

In another embodiment, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and one or more vehicles to obtain a plastically deformable mass;
(b) extruding the mixture obtained in step (a) to obtain cylindrical extrudates having desired length and diameter to form immediate release components in the form of extrudates;
(c) optionally, spheronizing the extrudates to form immediate release components in the form of spherical pellets;
(d) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;
(e) optionally, coating a barrier layer over the methylphenidate layered particles;
(f) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component; and
(g) filling the immediate release component prepared in step (b) or (c) and extended release component prepared in step (f) in a capsule.

In a further embodiment, the process of manufacturing a modified release methylphenidate composition comprises the steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;
(b) granulating the mixture prepared in step (a) followed by compression to form immediate release component in the form of mini-tablets;
(c) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;
(d) granulating the mixture prepared in step (c) to form matrix type extended release component;

(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

In another general aspect, there is provided a process for preparation of a modified release capsule, which process comprises steps of:
(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and one or more vehicles to obtain a plastically deformable mass;
or processing methylphenidate or salts thereof along with one or more polymer to form a molten mass;
(b) extruding the mixture or molten mass obtained in step (a) to obtain cylindrical extrudates having desired length and diameter to form immediate release components in the form of extrudates;
(c) optionally, spheronizing the extrudates to form immediate release components in the form of spherical pellets;
(d) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;
or processing methylphenidate or salts thereof along with one or more rate controlling substances to form a molten mass;
(e) granulating the mixture prepared in step (d) to form matrix type extended release components;
or extruding the molten mass obtained in step (d) to obtain extended release components in the form of cylindrical extrudates having desired length and diameter;
(f) optionally spheronizing the extrudates prepared in step (e) to form extended release components in the form of pellets
(g) filling the immediate release components prepared in step (b) or (c) and the extended release components prepared in step (e) or (f) in a capsule.

An aqueous or a pharmaceutically acceptable solvent medium may be used for preparing methylphenidate containing granules. Binder for preparing extended release component of methylphenidate may be selected from water soluble, alcohol soluble or acetone/water soluble binders are used. Binders such as

polyvinylpyrrolidone (PVP), polyethylene oxide, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polysaccharides such as dextran, corn starch may be used at concentrations of 0.5 to 5% w/w. Methylphenidate may be present in the extended release component up to 55% w/w, preferably up to about 40% w/w, and most preferably up to about 20% w/w.

The modified release composition of methylphenidate or salts thereof may be developed in the form a capsule, a tablet, a caplet and a mini-tablet. Preferably the dosage form is in the form of a capsule.

In an embodiment, the modified release composition in accordance of the present invention is in the form of a hard gelatin capsule filled with granules comprising methylphenidate or salts thereof and one or more pharmaceutically acceptable excipients, and plurality of pellets comprising matrix of methylphenidate or salts thereof and one or more rate controlling substances.

The term "pharmaceutically acceptable excipients" includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering an active pharmaceutical ingredient. Each excipient should be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Excipients include diluents, binders, disintegrants, glidants, lubricants, flavoring, and others.

The composition of the present invention may comprise one or more pharmaceutically acceptable excipients selected from, but not limited to, diluent, binder, disintegrant, glidant, lubricant, stabilizing agent, and flavoring agents.

Diluents increase the bulk of a solid pharmaceutical composition. Exemplary diluents for solid compositions include, but are not limited to, microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide,

maltodextrin, mannitol, polymethacrylates, potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compressed may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Exemplary binders for solid pharmaceutical compositions include, but are not limited to, acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone, pregelatinized starch, sodium alginate and starch.

Disintegrants increase the dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach, for example. Exemplary disintegrants include, but are not limited to, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Exemplary excipients that may function as glidants include, but not limited to, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Exemplary lubricants include, but are not limited to, magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

The present invention further provides a method of treating a method of treating ADD or ADHD by administering the patient in need thereof the modified release pharmaceutical composition of methylphenidate or salts thereof as substantially described throughout the specification.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

**Example 1: Methylphenidate Extended Release Capsule**

**Table 1**

| Sr. No. | Ingredient | Mg/cap |
|---|---|---|
| **Immediate release granules – Part I** | | |
| 1 | Methylphenidate | 18 |
| 2 | Microcrystalline Cellulose | 42 |
| | **Total weight** | 60 |
| **Matrix pellet – Part II** | | |
| 3 | Methylphenidate | 42 |
| 4 | Microcrystalline Cellulose | 58 |
| 5 | Hypromellose K4M CR | 60 |
| 6 | Hypromellose K15M CR | 60 |
| | **Total weight** | **220** |
| **Seal coating** | | |
| 7 | Opadry clear YS1R7006 | 4.4 |
| | **Total weight** | **224.4** |
| 8 | Size '0' EHGC | **1** |
| | **Total weight** | **284.4** |

**Process:** A mixture of Methylphenidate and Microcrystalline Cellulose was blended in a rotary mixer granulator. The blend was granulated with water in a rotary mixer granulator. The granules were dried and sifted through sieve of suitable mesh size. A mixture of Methylphenidate, Polyvinylpyrrolidone, Hypromellose K4M CR and Hypromellose K15M CR was granulated with water in rotary mixer granulator. The mass was extruded through 1.0mm bore size. The resulting extrudates were then spheronized at optimum speed to form pellets/extrudates. The pellets were then seal coated and dried. The granules and pellets were filled in size '0' hard gelatin capsules.

**Example 2: Methylphenidate Extended Release Capsule**

**Table 2**

| Sr. No. | Ingredient | Mg/cap |
|---|---|---|
| **Immediate release powder – Part I** | | |
| 1 | Methylphenidate | 18 |
| 2 | Microcrystalline Cellulose | 42 |
| | **Total weight** | **60** |
| **Drug loading and functional coating – Part II** | | |
| 3 | Methylphenidate | 42 |
| 4 | Sugar sphere | 158 |
| 5 | Polyvinylpyrrolidone | 2.1 |
| | **Total weight** | 202.1 |
| **Seal coating** | | |
| 6 | Opadry clear YS1R7006 | 6 |
| | **Total weight** | **208.1** |
| **Sustained release coating on Part II Functional coated pellet** | | |
| 7 | Ethyl cellulose* | 18.729 |
| 8 | Dibutyl sebacetate | 2.081 |
| | **Total weight** | **228.91** |

| | | |
|---|---|---|
| 8 | Size '0' EHGC | 1 |
| | **Total weight** | **288.91** |

* Dry polymer weight – calculation to be done based on dispersion quantity

**Process:** Methylphenidate and Microcrystalline Cellulose were mixed in a double cone blender to form powder blend. A solution of Methylphenidate and Polyvinylpyrrolidone was sprayed on sugar spheres using fluid bed coater. The drug loaded pellets were further seal coated using opadry clear in fluid bed coater. The seal coated Pellets are further coated using ethyl cellulose and dibutyl sebacetate based coating in fluid bed coater to form pellets. The powder blend and pellets were filled in size '0' hard gelatin capsules.

**Example 3: Methylphenidate Extended Release Capsule**

**Table 3**

| Sr. No. | Ingredient | Mg/cap |
|---|---|---|
| **Immediate release granules – Part I** | | |
| 1 | Methylphenidate | 18 |
| 2 | Microcrystalline Cellulose | 42 |
| | **Total weight** | **60** |
| **Drug loading and functional coating – Part II** | | |
| 3 | Methylphenidate | 42 |
| 4 | Sugar sphere | 158 |
| 5 | Polyvinylpyrrolidone | 2.1 |
| | **Total weight** | 202.1 |
| **Seal coating** | | |
| 6 | Opadry clear YS1R7006 | 6 |
| | **Total weight** | **208.1** |
| **Sustained release coating on Part II Functional coated pellet** | | |
| 7 | Ethyl cellulose* | 18.729 |

| | | |
|---|---|---|
| 8 | Dibutyl sebacetate | 2.081 |
| | **Total weight** | **228.91** |
| 9 | Size '0' EHGC | 1 |
| | **Total weight** | **288.91** |

* Dry polymer weight – calculation to be done based on dispersion quantity

**Process:** A mixture of Methylphenidate and Microcrystalline Cellulose was blended in a rotary mixer granulator. The blend was granulated with water in a rotary mixer granulator. The granules were dried and sifted through sieve of suitable mesh size. A solution of Methylphenidate and Polyvinylpyrrolidone was sprayed on sugar spheres using fluid bed coater. The drug loaded pellets were further seal coated using opadry clear in fluid bed coater. The seal coated Pellets are further coated using ethyl cellulose and dibutyl sebacetate based coating in fluid bed coater to form pellets. The granules and pellets were filled in size '0' hard gelatin capsules.

**Example 4: Methylphenidate Extended Release Capsule**

**Table 4**

| Sr. No. | Ingredient | Mg/cap |
|---|---|---|
| **Immediate release mini-tablets – Part I** | | |
| 1 | Methylphenidate | 18 |
| 2 | Microcrystalline Cellulose | 21 |
| 3 | Lactose monohydrate | 21 |
| | **Total weight** | **60** |
| **Drug loading and functional coating – Part II** | | |
| 4 | Methylphenidate | 42 |
| 5 | Sugar sphere | 158 |
| 6 | Polyvinylpyrrolidone | 2.1 |
| | **Total weight** | 202.1 |

| Seal coating | | |
|---|---|---|
| 7 | Opadry clear YS1R7006 | 6 |
| | **Total weight** | **208.1** |
| **Sustained release coating on Part II Functional coated pellet** | | |
| 8 | Ethyl cellulose* | 18.729 |
| 9 | Dibutyl sebacetate | 2.081 |
| | **Total weight** | **228.91** |
| 10 | Size '0' EHGC | 1 |
| | **Total weight** | **288.91** |

* Dry polymer weight – calculation to be done based on dispersion quantity

**Process:** A mixture of Methylphenidate, Lactose monohydrate and Microcrystalline Cellulose was blended in a rotary mixer granulator. The blend was granulated with water in a rotary mixer granulator. The granules were dried and sifted through sieve of suitable mesh size and compressed to form mini-tablets. A solution of Methylphenidate and Polyvinylpyrrolidone was sprayed on sugar spheres using fluid bed coater. The drug loaded pellets were further seal coated using opadry clear in fluid bed coater. The seal coated Pellets are further coated using ethyl cellulose and dibutyl sebacetate based coating in fluid bed coater to form pellets. The mini-tablets and pellets were filled in size '0' hard gelatin capsules.

**Example 5: Methylphenidate Extended Release Capsule**

**Table 5**

| Sr. No. | Ingredient | Mg/cap |
|---|---|---|
| **Immediate release mini-tablets – Part I** | | |
| 1 | Methylphenidate | 18 |
| 2 | Microcrystalline Cellulose | 21 |
| 3 | Lactose monohydrate | 21 |
| | **Total weight** | **60** |

| Matrix Pellet – Part II | | |
|---|---|---|
| 3 | Methylphenidate | 42 |
| 4 | Microcrystalline Cellulose | 58 |
| 5 | Hypromellose K4M CR | 60 |
| 6 | Hypromellose K15M CR | 60 |
| | **Total weight** | **220** |
| **Seal coating** | | |
| 7 | Opadry clear YS1R7006 | 4.4 |
| | **Total weight** | **224.4** |
| 8 | Size '0' EHGC | **1** |
| | **Total weight** | **284.4** |

**Process:** A mixture of Methylphenidate, Lactose monohydrate and Microcrystalline Cellulose was blended in a rotary mixer granulator. The blend was granulated with water in a rotary mixer granulator. The granules were dried and sifted through sieve of suitable mesh size and compressed to form mini-tablets. A mixture of Methylphenidate, Polyvinylpyrrolidone, Hypromellose K4M CR and Hypromellose K15M CR was granulated with water in rotary mixer granulator. The mass was extruded through 1.0mm bore size. The resulting extrudates were then spheronized at optimum speed to form pellets/extrudates. The pellets were then seal coated and dried. The mini-tablets and pellets were filled in size '0' hard gelatin capsules.

**Example 6: Methylphenidate Extended Release Capsule**

**Table 6**

| Sr. No. | Ingredient | Mg/cap |
|---|---|---|
| **Extrusion and Spheronization (IR extrude) – Part I** | | |
| 1 | Methylphenidate | 18 |
| 2 | Microcrystalline Cellulose | 62 |
| | **Total weight** | **80** |

| Matrix Pellet – Part II | | |
|---|---|---|
| 3 | Methylphenidate | 42 |
| 4 | Microcrystalline Cellulose | 58 |
| 5 | Hypromellose K4M CR | 60 |
| 6 | Hypromellose K15M CR | 60 |
| | **Total weight** | **220** |
| **Seal coating** | | |
| 7 | Opadry clear YS1R7006 | 4.4 |
| | **Total weight** | **224.4** |
| 8 | Size '0' EHGC | **1** |
| | **Total weight** | **304.4** |

**Process:** A mixture of Methylphenidate and Microcrystalline Cellulose was blended in a rotary mixer granulator. The blend was blended with water and the wet mass was extruded through 1.0mm bore size, followed by spheronization at optimum speed to from extrudates. The extrudates were dried and sifted through sieve of suitable mesh size. A mixture of Methylphenidate, Polyvinylpyrrolidone, Hypromellose K4M CR and Hypromellose K15M CR was granulated with water in rotary mixer granulator. The mass was extruded through 1.0mm bore size. The resulting extrudates were then spheronized at optimum speed to form pellets/extrudates. The pellets were then seal coated and dried. The extrudates and pellets were filled in size '0' hard gelatin capsules.

**Claims:**

1. A modified release pharmaceutical composition comprising at least one immediate release and at least one extended release component comprising methylphenidate or salts thereof, wherein the immediate release component is not in the form of core particles coated with layer of methylphenidate.

2. A modified release pharmaceutical composition comprising at least one immediate release and at least one extended release component comprising methylphenidate or salts thereof, wherein the extended release component is not in the form of core particles coated with layer of methylphenidate.

3. The modified release pharmaceutical composition of claim 1 or 2, wherein the immediate release component is in the form selected from the group of mixture, granules, pellets, mini-tablets and extrudates of methylphenidate and one or more pharmaceutically acceptable excipients, or combinations thereof.

4. The modified release pharmaceutical composition of claim 2, wherein the extended release component is in the form selected from-
   (i) core particles coated with one or more layers of methylphenidate, which is further coated with one or more rate controlling substances;
   (ii) matrix of methylphenidate, and one or more rate controlling substances; or
   (iii) extrudates of methylphenidate, and one or more rate controlling substances.

5. The modified release pharmaceutical composition of claim 2, wherein the extended release component is in the form selected from-
   (i) matrix of methylphenidate, and one or more rate controlling substances; or
   (iii) extrudates of methylphenidate, and one or more rate controlling substances.

6. The modified release pharmaceutical composition of claim 1 or 2, wherein the immediate release and/or extended release components are in the form selected from the group of tablets, mini-tablets, granules, pellets, spheroids, beads or combination thereof.

7. The modified release pharmaceutical composition of claim 1 or 2, wherein the composition is characterized in that it retains at least 90% w/w of the potency of methylphenidate or salts thereof when stored at $40^0$C and 60% relative humidity for 3 months.

8. The modified release pharmaceutical composition of claim 1, wherein the composition is bioequivalent to the methylphenidate formulation marketed under the trade name Metadate CD®.

9. A capsule comprising the modified release pharmaceutical composition of claim 1, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form immediate release component in the form of a dry blend;

(b) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;

(c) optionally, coating a barrier layer over the methylphenidate layered particles;

(d) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component;

(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

10. A capsule comprising the modified release pharmaceutical composition of claim 1, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and granulating with a vehicle to form granules as an immediate release component

(b) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;

(c) optionally, coating a barrier layer over the methylphenidate layered particles;

(d) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component;

(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

11. A capsule comprising the modified release pharmaceutical composition of claim 1, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;

(b) granulating the mixture prepared in step (a) followed by compression to form immediate release component in the form of mini-tablets;

(c) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;

(d) optionally, coating a barrier layer over the methylphenidate layered particles;

(e) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component; and

(f) filling the immediate release component prepared in step (b) and the extended release component prepared in step (e) in a capsule.

12. A capsule comprising the modified release pharmaceutical composition of claim 1, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and one or more vehicles to obtain a plastically deformable mass;

or processing methylphenidate or salts thereof along with one or more polymer to form a molten mass;

(b) extruding the mixture or molten mass obtained in step (a) to obtain cylindrical extrudates having desired length and diameter to form immediate release components in the form of extrudates;

(c) optionally, spheronizing the extrudates to form immediate release components in the form of spherical pellets;

(d) coating inert core particles with one or more layers comprising methylphenidate and one or more pharmaceutically acceptable excipients to form methylphenidate layered particles;

(e) optionally, coating a barrier layer over the methylphenidate layered particles;

(f) coating the methylphenidate layered particles with one or more layers comprising one or more rate controlling substances to form extended release component; and

(g) filling the immediate release component prepared in step (b) or (c) and extended release component prepared in step (f) in a capsule.

13. A capsule comprising the modified release pharmaceutical composition of claim 1, 2 or 3, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;

(b) granulating the mixture prepared in step (a) to form immediate release component in the form of granules;

(c) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;

(d) granulating the mixture prepared in step (c) to form extended release component;

(e) filling the immediate release component prepared in step (a) and the extended release component prepared in step (d) in a capsule.

14. A capsule comprising the modified release pharmaceutical composition of claim 1, 2 or 3, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients to form a mixture;

(b) granulating the mixture prepared in step (a) followed by compression to form immediate release component in the form of mini-tablets;

(c) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;

(d) granulating the mixture prepared in step (c) to form matrix type extended release component;

(e) filling the immediate release component prepared in step (b) and the extended release component prepared in step (d) in a capsule.

15. A capsule comprising the modified release pharmaceutical composition of claim 1, 2 or 3, wherein the composition is prepared by a process, which process comprises steps of:

(a) mixing methylphenidate or salts thereof with one or more pharmaceutically acceptable excipients and one or more vehicles to obtain a plastically deformable mass;

or processing methylphenidate or salts thereof along with one or more polymer to form a molten mass;

(b) extruding the mixture or molten mass obtained in step (a) to obtain cylindrical extrudates having desired length and diameter to form immediate release components in the form of extrudates;

(c) optionally, spheronizing the extrudates to form immediate release components in the form of spherical pellets;

(d) mixing methylphenidate or salts thereof with one or more rate controlling substances, and optionally pharmaceutically acceptable excipients to form a mixture;

or processing methylphenidate or salts thereof along with one or more rate controlling substances to form a molten mass;

(e) granulating the mixture prepared in step (d) to form matrix type extended release components;

or extruding the molten mass obtained in step (d) to obtain extended release components in the form of cylindrical extrudates having desired length and diameter;

(f) optionally spheronizing the extrudates prepared in step (e) to form extended release components in the form of pellets

(g) filling the immediate release components prepared in step (b) or (c) and the extended release components prepared in step (e) or (f) in a capsule.

16. A hard gelatin capsule filled with one or more tablets, mini-tablets, granules, pellets, spheroids or beads comprising methylphenidate or salts thereof and one or more pharmaceutically acceptable excipients, and one or more tablets, mini-tablets, granules, pellets, spheroids, beads comprising methylphenidate or salts thereof and one or more rate controlling substances, wherein the immediate release component and/or the extended release component is not in the form of core particles coated with layer of methylphenidate.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060084

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4458 A61K9/16 A61K9/50
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/00213 A1 (TEVA PHARMA [IL]; TEVA PHARMA [US]; FLESHNER BARAK MOSHE [IL]; LERNER) 3 January 2002 (2002-01-03) page 18 - page 19; claims 90,91 | 1-8,16 |
| X | WO 99/62496 A1 (ALZA CORP [US]) 9 December 1999 (1999-12-09) claims; figures; examples | 1-8 |
| X | US 2012/207824 A1 (MEHTA KETAN [US] ET AL) 16 August 2012 (2012-08-16) claim 26; examples | 1-8,16 |
| X | US 5 837 284 A (MEHTA ATUL M [US] ET AL) 17 November 1998 (1998-11-17) claims; examples | 1-16 |

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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