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(54) Title: TROSPIUM PHARMACEUTICAL FORMULATIONS

(57) Abstract: Controlled release pharmaceutical compositions comprising trospium or pharmaceutically acceptable salts thereof and one or more release controlling components, wherein the composition is in monolithic form, reservoir form, multiparticulate form, or a combination thereof.

TROSPIUM PHARMACEUTICAL FORMULATIONS

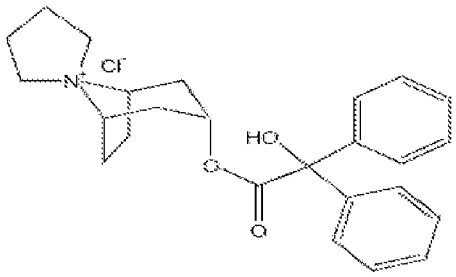
INTRODUCTION

The present invention relates to pharmaceutical compositions comprising trospium, including pharmaceutically acceptable salts thereof. More specifically, the present invention relates to controlled release pharmaceutical compositions comprising trospium or pharmaceutically acceptable salts thereof, for therapeutic purposes, and methods of preparing the same.

Trospium chloride is an agent that has been known for many years (e.g., from German Patent No. 1 194 422) as an anticholinergic that is useful as a spasmolytic agent. The active agent has been commercially available in an orally administrable solid form as tablets, for intravenous or intramuscular injection as a solution, and for rectal administration as suppositories. It is mainly used for the treatment of bladder dysfunctions. The product has been available in Germany and several other European countries for a number of years for specific therapeutic indications including urinary frequency, urgency, nocturia, and urge-incontinence associated with detrusor instability, urge syndrome, and detrusor hyperreflexia.

Trospium chloride is a quaternary ammonium derivative of tropine. The hydrophilicity of the molecule, due to its permanent positive charge, limits its lipid solubility. Trospium has been shown to reduce bladder hyperactivity in patients suffering from urinary incontinence and exerts spasmolytic effects on the bladder by inhibiting the effects of acetylcholine on smooth muscle. It has selectivity for muscarinic receptors over nicotinic receptors and as a result, no blocking effects are observed at skeletal neuromuscular junctions. Thus, this anticholinergic drug trospium chloride can also be called an antimuscarinic drug. Active metabolites of trospium chloride exert antimuscarinic activities that are believed to account for part of the therapeutic activity of trospium.

Trospium chloride was disclosed in U.S. Patent No. 3,480,626 where it was said to have excellent spasmolytic properties. Trospium chloride has chemical names 3α–hydroxy-spiro [1αH,5αH-nortropane-8,1'-pyrrolidinium]- chloride benzilate, or spiro[8-azoniabicyclo[3,2,1]octane-8,1'-pyrrolidinium]-3-[(hydroxydienyl-acetyl)-oxy]chloride(1α,3β,5α)-(9Cl), a molecular formula $C_{25}H_{30}ClNO_3$, and is represented by structural Formula I.



Formula I

Trospium chloride is approved in many countries for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. Currently, in the U.S. market there is an immediate release trospium chloride tablet (SANCTURA®), provided as a 20 mg tablet and administered twice daily for a total dose of 40 mg per day. Recently U.S. Food and Drug Administration has given approval for extended release trospium chloride 60 mg capsules (SANCTURA® XR) for once-daily administration.

U.S. Patent Application Publication No. 2006/0217405 A1 describes a method for the treatment or prophylaxis of interstitial cystitis using anti-muscarinic agents such as trospium chloride.

U.S. Patent No. 5,998,430 describes compositions of trospium chloride in the form of a sterile, aqueous solution that is prepared prior to administration, suitable for localized administration directly into the bladder.

Orally administered, trospium chloride is slowly absorbed, with the maximum blood concentration achieved after 5-6 hours. The oral bioavailability is approximately 10%, and is significantly reduced with the intake of high-fat food. There are side effects associated with the use of the twice-daily trospium chloride regimen, such as dry mouth, headache, constipation, dyspepsia, and abdominal pain. These side effects are associated with a high blood concentration of trospium chloride. Moreover, studies in which a 40 mg immediate release dose was given once daily resulted in higher overall incidence of adverse events as compared to 20 mg given twice daily. Hence, there is a need for a controlled release formulation of trospium chloride to reduce the overall incidence of adverse events associated with a high blood concentration of trospium chloride and to provide therapeutic concentrations throughout the day for the treatment of overactive bladder and other such disorders. This is advantageous in terms of

both patient compliance and reduced adverse events, thus providing better treatment of the conditions for which it is indicated.

U.S. Patent No. 5,700,410 discloses a process for preparing a wax matrix for controlled release of drugs, using a multi-screw extruder.

U.S. Patent Application Publication No. 2004/0028729 describes a roller compacting method to prepare irregularly shaped nonspherical cores, used for sustained release pharmaceutical preparations.

U.S. Patent Application Publication No. 2005/0191351 A1 describes once-daily dosage forms of trospium, which upon administration to a human patient generate average steady state blood concentrations of trospium with minimum (C_{min}) and maximum (C_{max}) blood levels of about 0.5-2.5 ng/mL and about 2.0-6.0 ng/mL, respectively.

U.S. Patent Application Publication No. 2005/0123606 A1 describes compositions of quaternary ammonium compounds containing bioavailability enhancers.

U.S. Patent Application Publication No. 2006/0210625 A1 discloses sustained release of positively charged pharmacologically active molecules such as trospium chloride from a matrix containing polymers with polarized oxygen atoms.

There remains a need for alternative controlled release pharmaceutical compositions comprising trospium chloride in order to reduce the adverse events and dosing frequency, thereby improving patient compliance.

SUMMARY

The present invention relates to controlled release pharmaceutical compositions comprising trospium, including pharmaceutically acceptable salts thereof, for therapeutic purposes, and methods of preparing the same.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or pharmaceutically acceptable salts thereof and one or more drug release controlling non-polymeric components.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or pharmaceutically acceptable salts thereof and at least one release controlling non-polymeric component comprising waxes, waxy materials, ion-exchange resins, and combinations thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or pharmaceutically acceptable salts thereof and one or more release controlling non-polymeric components, wherein the composition is in monolithic form, reservoir form, multiparticulate form, or any combinations thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or pharmaceutically acceptable salts thereof, wherein the compositions release substantially greater amounts of the contained trospium into the upper part of the gastrointestinal tract.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof, wherein the compositions are in the form of capsules, and are bioequivalent when administered as intact capsules, or having opened capsule contents sprinkled onto soft food or juice, to a human subject in need thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more release controlling non-polymeric components, wherein the compositions are in the form of capsules and are bioequivalent to the commercial product SANCTURA® XR capsules, when both capsule contents are sprinkled onto soft food or juice, before being administered to a human subject in need thereof.

In another embodiment, the invention includes methods of preparing pharmaceutical compositions of the present invention.

In a further embodiment the invention includes methods of treating patients suffering from overactive bladder with symptoms of urge urinary incontinence, urgency, urinary frequency, nocturia, and urge-incontinence associated with detrusor instability, urge syndrome, and detrusor hyperreflexia using pharmaceutical compositions of the present invention.

In an aspect, the invention provides a pharmaceutical formulation comprising trospium or a salt thereof and at least one of a wax material and an ion exchange resin, releasing less than about 90 percent of contained trospium within about 6 hours after immersion into an aqueous fluid.

In another aspect, the invention provides a process for preparing a pharmaceutical formulation, comprising combining trospium or a salt thereof with a wax material or an ion exchange resin to obtain a formulation that releases less

than about 90 percent of contained trospium within about 6 hours after immersion into an aqueous fluid.

DETAILED DESCRIPTION

The present invention relates to controlled release pharmaceutical compositions comprising trospium, including pharmaceutically acceptable salts thereof, for oral administration, and methods of preparing the same.

As used herein the term “trospium” includes the compound trospium, pharmaceutically acceptable salts of trospium, prodrugs thereof, active metabolites of trospium, prodrugs thereof, and their polymorphs, solvates and hydrates.

The terms "pharmaceutically acceptable salt" refers to salts of trospium and active metabolites of trospium, and said salts may be prepared using pharmaceutically acceptable acids. Suitable pharmaceutically acceptable salts include but are not limited to the chloride and other halogen salts, and salts such as are formed by reaction of trospium with acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pathothenic, phosphoric, p-toluenesulfonic, succinic, sulfuric, and tartaric acids, and the like. For simplicity, the invention frequently will be discussed hereafter using trospium chloride, which is a fine, colorless to slightly yellow, crystalline solid having solubility in water of approximately 1 g/2 mL.

According to the present invention, trospium and its salts can be used in any crystalline form, or in amorphous form, or in combinations thereof.

As used herein the term "controlled release" means the release of the active substance, i.e., trospium chloride, from a pharmaceutical dosage form in a manner modified to occur at a different time and/or at a different rate than that obtained from an immediate release product, such as a conventional swallowed tablet or capsule. Sometimes the active substance may be present in "sustained release" form where the release of the active substance is modified to occur over a prolonged period of time. Sometimes the active substance may be present in "delayed release" form where the release of the active substance is modified to commence at a later time than that from an immediate release form. Controlled

release compositions can exhibit sustained release characteristics, delayed release characteristics, or a combination thereof.

Controlled release pharmaceutical compositions of the present invention release drug over periods of time at least about 6 hours, or at least about 8 hours, or at least about 12 hours, or at least about 16 hours, or at least about 20 hours, following administration.

In embodiments, the pharmaceutical compositions release less than about 90 percent of contained trospium within about 6 hours after immersion into an aqueous fluid. An aqueous fluid for determining drug release generally has a physiologically relevant pH value, i.e., from about 1 to about 8.

As used herein the term “release controlling non-polymeric component“ means any component that functions to control the release of active substance form the compositions of the present invention and is not polymeric in nature. Examples of such components include waxes, waxy materials, ion-exchange resins, or combinations thereof. In the following discussion, the term "wax" is used for any suitable wax or waxy material.

A pharmaceutical composition according to the present invention can be presented in forms such as tablets, multilayered tablets, capsules, granules, spheroids, beads, pellets, minitablets, powders, sachets, gels, dispersions, solutions, or suspensions.

As used herein the term “particulate“ includes granules, spheroids, beads, pellets, and minitablets.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium and one or more release controlling non-polymeric components.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium and at least one release controlling non-polymeric component comprising waxes, waxy materials, ion-exchange resins, and combinations thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium and one or more release controlling non-polymeric components wherein said composition is in monolithic form, reservoir form, multiparticulate form, or any combinations thereof.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium and one or more waxes as release controlling components.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium, wherein trospium is embedded in a matrix comprising one or more waxes.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium, wherein trospium is embedded in a matrix comprising one or more waxes, and the compositions are in monolithic form.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium, one or more waxes and optionally other additives, wherein trospium is uniformly distributed or embedded in a wax matrix, and the compositions are in monolithic form.

In an embodiment, the invention includes controlled release pharmaceutical compositions which are uncoated.

In another embodiment, pharmaceutical compositions of the invention optionally have one or more coatings which are functional or nonfunctional. Functional coatings include controlled release coatings such as delayed release coatings, and non-functional coatings include seal coatings and aesthetic coatings.

In one embodiment, the optional functional coating comprises one or more polymers.

In another embodiment, pharmaceutical compositions are optionally coated with a composition comprising trospium or a salt thereof.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium, wherein trospium is embedded in a matrix comprising one or more waxes, and said compositions are in multiparticulate form.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising controlled release multiparticulates, wherein each particle comprises trospium and one or more waxes.

In one embodiment, controlled release multiparticulates comprising trospium include cores comprising trospium and one or more waxes, and optionally other additives.

In one embodiment, multiparticulates comprising trospium are uncoated. In other embodiments, multiparticulates comprising trospium chloride contain one or more coatings over cores.

In still other embodiments, multiparticulates comprising trospium have a non-functional seal coating, or a functional coating, or both.

In one embodiment, a functional coating of multiparticulates comprises one or more polymers.

In one embodiment, an initial seal coating can be applied directly to cores.

Optionally, multiparticulates contain a further coating layer comprising one or more waxes over an initial seal coating, if present, or directly over uncoated multiparticulate trospium-containing cores, to provide further control of drug release.

In still other embodiments, any one or all of the coating compositions optionally contain trospium or a salt thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein trospium is present in reservoir form.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising cores comprising trospium or a salt thereof and a coating comprising one or more waxes, and said compositions are in monolithic form.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising cores comprising a pharmaceutically acceptable additive, and a coating comprising trospium or a salt thereof, wherein said compositions are in monolithic form.

In one embodiment, the invention includes controlled release pharmaceutical compositions optionally having one or more further coatings which are functional or non-functional. Functional coatings include controlled release coatings, and non-functional coatings include seal coatings and aesthetic coatings.

In one embodiment, a functional coating comprises one or more polymers.

In another embodiment, the invention includes controlled release pharmaceutical compositions optionally having a further coating comprising trospium or a salt thereof.

Wax-based compositions of the present invention may be prepared using processes including fusion methods, spray methods, fusion-spray methods, or hot melt extrusion methods, such as are well known in the art.

Compositions of the present invention may be prepared using process steps including one or more of wet granulation, melt granulation, dry granulation such as slugging or compaction, direct compression, and various coating processes, and are formulated into dosage forms including tablets and capsules.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein trospium is present in reservoir form and the compositions are in multiparticulate form.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising cores comprising trospium or a salt thereof and a coating comprising one or more waxes, and said compositions are in multiparticulate form.

In one embodiment, controlled release multiparticulates comprising trospium are composed of cores comprising trospium and optionally one or more pharmaceutically acceptable additives, and a coating comprising one or more waxes.

In one embodiment, controlled release multiparticulates comprising trospium are composed of non-pariel cores such as inert sugar or similar substances, upon which trospium or a salt thereof is loaded optionally along with other pharmaceutically acceptable additives, using any technique such as powder layering, solution spraying, or suspension spraying.

In one embodiment, controlled release compositions of the invention are composed of trospium loaded non-pariel cores having a coating comprising one or more waxes.

In another embodiment, the invention includes pharmaceutical compositions comprising controlled release multiparticulates comprising trospium, composed of drug containing cores and a coating comprising one or more waxes, and optionally having one or more further coatings.

In still other embodiments, the multiparticulates comprising trospium further contain a non-functional seal coating, a functional coating, or both.

In one embodiment, a functional coating of multiparticulates comprises one or more polymers

In one embodiment, an initial seal coating can be applied directly to drug containing cores.

In embodiments, any one or all of the coating compositions optionally contain trospium or a salt thereof.

Multiparticulate formulations of the invention can be prepared using the techniques described herein, as well as other methods known to those having skill in the art.

In embodiments, multiparticulates comprising trospium are coated with different concentrations of waxes, giving different release profiles, and can be combined to form a pharmaceutical composition or dosage form to achieve desired controlled release profiles.

In embodiments, multiparticulates comprising trospium or a salt thereof are combined with a pharmaceutically acceptable carrier and optionally other additives, and compounded to form a pharmaceutical composition, i.e., can be compressed into tablets or placed into suitable capsule shells, using techniques known to those having skill in the art.

In embodiments, the invention includes controlled release pharmaceutical compositions comprising about 10 to 25% by weight of trospium or a salt thereof and about 30 to 80% by weight of one or more waxes.

Waxes that can be used in the present invention include waxes of animal or vegetable origin, synthetic waxes and semisynthetic waxes. They include waxes that are solid at room temperature such as higher fatty acids, higher fatty acid ester derivatives, higher alcohols and higher alcohol ester derivatives. Examples of waxes include conventional waxes and waxy materials such as carnuba wax, spermaceti wax, candellila wax, cocoa butter, beeswax, paraffin, partially hydrogenated vegetable oils, hydrogenated vegetable oils, ceresin, higher fatty acids such as stearic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, margaric acid, nonadecanoic acid, arachidonic acid, behenic acid, lignoceric acid, cerotic acid, and montanic acid, higher fatty acid ester derivatives such as glyceryl, ethylene glycol, propylene glycol, sorbitol, polyethylene glycol and other esters of the above fatty acids, saturated fatty acid glycerides derived from animals or vegetables, mixtures thereof, and

hydrogenated oils available from said glycerides of animal or vegetable origin, glycerides of oleic acid, linolic acid, linolenic acid, ricinoleic acid, etc. and mixtures thereof, higher alcohols such as cetosteryl alcohol, myristyl alcohol, stearyl alcohol, cetyl alcohol, pentadecanol, hexadecanol, heptadecanol, octadecanol, nonadecanol, eicosanol, and wool alcohol, cholesterol, higher alcohol ester derivatives such as cholesteryl palmitate, glyceryl monostearate and phytosterol palmitate, glyceryl palmitostearate, glyceryl behenate, diethyleneglycol palmitostearate, polyethyleneglycol stearate, polyethyleneglycol palmitostearate, polyoxyethylene-glycol palmitostearate, glyceryl monopalmitostearate, cetyl palmitate; saturated or unsaturated fatty acids and their hydrogenated derivatives, and lipophilic substances in general.

In an aspect the present invention provides processes for preparing compositions comprising trospium or a salt thereof and wax, wherein an embodiment comprises:

i) melting wax to form a clear liquid;

ii) adding trospium or a salt thereof to the liquid of step i) with stirring;

iii) cooling the mixture of step ii) with stirring until it solidifies;

iv) sifting the solidified matrix of step iii) through a sieve;

v) blending the sifted material of step iv) with optional extragranular additives such as diluents and glidants;

vi) adding a lubricant to the blend of step v); and

vii) compressing into tablets.

In embodiments the present invention provides pharmaceutical compositions comprising trospium in any forms including tablets, film-coated tablets, pellets, mini-tablets, powders, capsules filled with powders, pellets, mini-tablets, or one or more tablets, and combinations thereof.

In an embodiment the present invention includes a powder that can be can be filled into a capsule along with one or more of pellets, mini-tablets or tablets, wherein the powder comprises at least one component which includes trospium or a salt thereof, one or more release controlling non-polymeric components, one or more release controlling polymers and one or more pharmaceutically acceptable additives.

In an embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof, wherein said composition is in the form of capsules filled with one or more tablets.

In an embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein the composition is in the form of capsules filled with one or more tablets.

In an embodiment, more than one tablets filled into a capsule provide different release profiles of trospium or a salt thereof which includes immediate release, controlled release, delayed release, or combinations thereof.

In an embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein the compositions are in the form of capsules containing two or three tablets which provide different release profiles of trospium or a salt thereof.

In another embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof, wherein said compositions are in the form of capsules containing mini-tablets.

In one embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein the compositions are in the form of capsules containing mini-tablets.

In another embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein said composition is in the form of capsule containing one or more mini-tablets.

In an embodiment, one or more different mini-tablets filled into a capsule provide different release profiles of trospium or a salt thereof, which include immediate release, controlled release, delayed release, or combinations thereof.

In one embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein the compositions are in the form of capsules filled with one or more different mini-tablets which provide different release profiles of trospium or a salt thereof.

In another embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or

more waxes, wherein the compositions are in the form of capsules filled with multiparticulates.

In one embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein the compositions are in the form of capsules filled with one or more different multiparticulates.

In one embodiment, one or more different multiparticulates filled into capsules provide different release profiles of trospium or a salt thereof, which include immediate release, controlled release, delayed release or combinations thereof.

In one embodiment the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes, wherein the compositions are in the form of capsules filled with one or more different multiparticulates, which provide different release profiles of trospium or a salt thereof.

In embodiments, the invention includes controlled release pharmaceutical compositions comprising trospium and one or more waxes as release controlling components, wherein the compositions are bioequivalent to the commercial product SANCTURA® XR.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more ion-exchange resins as release controlling components.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more ion-exchange resins, wherein the resins control the release of trospium from dosage forms.

Ion exchange resins (hereinafter referred as “resins”) are water-insoluble polymers that contain acidic or basic functional groups and have the ability to exchange counter-ions with aqueous solutions surrounding them. When a drug is loaded onto or released from a resin, a drug ion and an inorganic ion are exchanged. This property allows drugs to be loaded onto resins (forming “drug resinates”) and then be released *in vivo* into gastrointestinal fluids. The drug resinates possess physical properties similar to those of the resin. These two

properties, drug release and physical properties, can be manipulated to create many variations of use.

The term “drug resinate” refers to trospium or a salt thereof in combination with an ion exchange resin. This resinate may be obtained by admixing the drug and resins in any manner and it can be used to prepare a variety of formulations. In most cases, the process of making resinate involves dissolving drug in a suitable solvent and then adding the resin. Loading or complexing of drug takes place at ambient or elevated temperatures and usually requires a few hours to complete. Resinate so formed is then isolated by filtration or by spray drying.

The "resins" herein used may be natural, semisynthetic or synthetic resins, which may be either thermoplastic or thermosetting resins. Ion exchange resins have been classified based on the charge on the exchangeable counter ion (cation exchanger or anion exchanger) and the ionic strength of the bound ion (strong exchanger or weak exchanger). Thus there are four primary types of ion exchange resins: strong cation exchange resins, containing sulfonic groups or the corresponding salts; weak cation exchange resins, containing carboxylic acid groups or the corresponding salts; strong anion exchange resins containing quaternary ammonium groups; and weak anion exchange resins, containing ammonium chloride or hydroxide. Commercially different grades of cationic exchange resins and anionic exchange resins are available, for example Amberlite and Duolite are registered trademarks of Rohm and Haas Company and Dowex is registered trademark of Dow Chemical Company.

Among the ion exchange resins that are useful in the present invention include styrene-divinylbenzene copolymers (e.g. Amberlite IRP 69, a strongly acidic sodium form cation exchange resin with sulfonic acid as active group; Amberlite IR 120, a strongly acidic hydrogen form gel-type resin with sulfonic acid as active group; Amberlite IRP 67, a strongly basic chloride form resin with $N(CH_3)_3^+Cl^-$ as an active group; Amberlite IRA 410, a strongly basic chloride form anion exchange gel-type resin with benzyldimethyl (2-hydroxyethyl)ammonium as active group; Amberlite IRA 400, a strongly basic chloride form gel-type resin with quaternary ammonium as active group), copolymers of methacrylic acid and divinylbenzene (e.g. Amberlite IRP 64, a weekly acidic, hydrogen form cation exchange resin with weak acid as active group; Amberlite IRP 88, an acrilin potassium resin), phenolic polyamines (e.g. Amberlite IRP58) and styrene-

divinylbenzene (e.g., colestyramine resin). It is also possible to use other types of ion exchange resins such as Dowex 1X2100, a chloride form strongly basic anion exchange resin with styrene-divinylbenzene as matrix and trimethylbenzyl ammonium as active group; Dowex 50 X2100, a hydrogen form strongly acidic cation exchange resin with nuclear sulfonic acid as active group; Duolite C-26, a cationic resin having polystyrene skeleton with sulfonic acid as active group; Duolite A-7, a weakly basic anion exchanger with polyamine as active group. The invention also includes mixed bed resins for example Dowex MR-3 UPW having styrene-divinyl benzene gel matrix with sulfonic acid and quaternary ammonium as active groups; Amberlite IRC-748 (iminodiacetic acid), having a polymeric matrix of copolymer of styrene-divinyl benzene with two active groups imino -N- and carboxylic .

Typical examples of resins include but are not limited to polyethylenes, polypropylenes, vinyl chloride resins, ABS resins, polyesters, polyvinylidine chlorides, polyamides, polystyrenes, polyacetals, polyvinyl alcohols, polycarbonates, acrylic resins, fluorine plastics, polyurethane elastomers, polyester elastomers, phenolic resins, urea resins, melamine resins, unsaturated polyester resins, epoxy resins, urethane resins, rayons, cuprammonium rayons, acetate resins, natural rubbers, synthetic rubbers and EVA resins. These resins may be used alone or in combination.

In an embodiment the invention includes weight ratios of drug to resin in the range of from about 1:1 to about 1:8, or from about 1:1 to about 1:6, or from about 1:1 to about 1:4, or from about 1:1 to about 1:2.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium and one or more ion-exchange resins wherein the resin provides a release of said trospium in the following ways: monophasic release, biphasic release, or triphasic release.

Furthermore, controlled release pharmaceutical compositions of trospium using resin can be formulated either as monolithic or as heterogeneous compositions and can be made into matrix systems, reservoir systems, or combinations of matrix and reservoir systems.

In aspects the present invention provides processes for preparing a composition comprising trospium and ion exchange resin, wherein an embodiment of a process comprises:

i) suspending a resin in solvent;

ii) adding trospium to the resin suspension;

iii) stirring the above dispersion for few hours;

iv) separating a solid resinate;

v) drying the drug-resinate; and

vi) sifting the drug resinate through a sieve.

In aspects, the present invention provides granulating processes for preparing compositions comprising trospium and an ion exchange resin, wherein an embodiment of a process comprises:

i) providing a solution comprising trospium;

ii) granulating a resin using the drug solution;

iii) drying the granules;

iv) optionally washing the drug-resin complex with solvent and drying; and

v) sifting the drug resin complex through a sieve.

In aspects the invention includes processes to prepare controlled release pharmaceutical compositions comprising drug resinates, wherein an embodiment of a process comprises:

i) sifting diluents, glidants, lubricants and any other desired excipients through a sieve;

ii) adding the sifted excipients, except lubricants, to a drug resinate prepared by a process described above and blending;

iii) adding lubricants and blending;

iv) compressing the final blend into tablets or filling into empty hard gelatin capsules; and

v) optionally, coating tablets.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and at least one wax and at least one ion-exchange resin as release controlling non-polymeric components.

Further, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and at least one wax and at least one ion-exchange resin, wherein a composition can be formulated either as monolithic or as a heterogeneous composition and can be made into matrix systems, reservoir systems, or combinations of matrix and reservoir systems.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and at least one wax and at least one ion-exchange resin as release controlling non-polymeric components, and said compositions are in multiparticulate form.

In an embodiment, wax based multiparticulates comprising trospium or a salt thereof, which will give different release profiles, can be combined with multiparticulates comprising trospium resinates to form pharmaceutical compositions or dosage forms to achieve a desired controlled release.

In another embodiment, the invention includes controlled release osmotic devices comprising: (a) cores comprising trospium, optionally osmotic agents and other pharmaceutically acceptable additives; (b) semipermeable walls surrounding the cores; and (c) optionally one or more passageways in the walls.

Osmotic agents that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across a semipermeable wall against an external fluid. Osmotic agents useful in the present invention include, without limitation thereto, one or more of sodium chloride, magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, d-mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, and mixtures thereof.

A semipermeable wall is permeable to the passage of an external fluid such as water and biological fluids, and is substantially impermeable to the passage of active agents, osmotic agents, and the like. Typical materials for forming a wall are exemplified by cellulose esters, cellulose ethers and cellulose ester-ethers. Representative materials include, without limitation thereto, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tri-cellulose alkanylates, mono-, di- and tri-cellulose aroylates, and the like.

A passageway as used herein comprises means and methods suitable for releasing the agent or drug from the osmotic system. A passageway includes at least one osmotic aperture or osmotic orifice through the semipermeable wall. Osmotic passageways can be formed by techniques including mechanical drilling or laser drilling.

The controlled release trospium compositions of the present invention are advantageous as they allow a more constant plasma concentration with reduced fluctuations over a prolonged period of time, when compared to an immediate-release composition, and avoid the necessity of administering trospium multiple times each day. This helps to alleviate side effects that are observed when immediate release trospium is administered.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof, wherein said composition releases substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

In another embodiment, the invention includes controlled release pharmaceutical composition comprising trospium or pharmaceutically acceptable salts thereof, wherein said composition releases at least about 60% by weight of the contained trospium into the upper part of the gastrointestinal tract.

By "upper part of gastrointestinal tract" is meant the portion of the gastrointestinal tract between the region of the mouth and the jejunum, inclusive.

The term “substantially greater amounts” in the invention refers to at least about 60%, or at least about 70%, or at least about 80%, and up to about 90%.

By “lower part of the gastrointestinal tract” is meant the portion of the gastrointestinal tract between the region of the ileum and the rectum, inclusive. In embodiments, the formulations of the invention release at least about 10 percent of contained trospium into a lower part of the gastrointestinal tract.

In an embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium or a salt thereof, wherein said gastro-retentive compositions achieve a prolonged stomach retention time and release substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

In another embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium, wherein said gastro-retentive compositions include a delivery system such as buoyant or floating systems, swelling or expanding systems, bioadhesive systems, high-density systems or combinations thereof, to achieve a prolonged stomach retention time, and release substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

The term "prolonged stomach retention time" in the invention refers to retention times of the dosage form in the stomach at least about 4 hours, or at least about 6 hours, or at least about 8 hours, or at least about 10 hours, after administration.

In another embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium or a salt thereof, wherein said gastro-retentive compositions are capable of floating on gastric fluid and release substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

Floating or buoyant systems are designed to have a low density and thus should float on gastric contents after administration until the system either disintegrates (and presumably resultant particles empty from the stomach) or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying.

Floating systems that can be used for the purpose of this invention include low density shells such as spherical polystyrene foam particles, in which drug and optionally release controlling component layers are loaded, and hydrodynamically balanced systems which have low density to enable floating on the stomach contents and which slowly eroded after administration, losing buoyancy and being expelled from the stomach. These systems comprise one or a mixture of hydrocolloids including cellulose derivatives such as methylcellulose, hydroxyalkylcelluloses and carboxymethylcelluloses, polycarbopils, or polyacrylates as carriers. Upon contact with gastric fluid, the hydrocolloids hydrate and acquire a bulk density of less than 1 g/mL, thereby being buoyant in the gastric fluid. The presence of pharmaceutically inert fatty materials having a specific gravity of less than one decreases the hydrophilicity and increases the buoyancy of the dosage forms.

Floating systems that can be used for the purpose of this invention also include expandable components which produce a gas such as, for example, carbon dioxide or nitrogen, on contact with gastric juice, in particular under the action of acid. Examples of these used according to the invention are carbonates and hydrogen carbonates of the alkali metals and alkaline earth metals, the ammonium cations or sodium azide, or mixtures thereof. These expandable

components can be optionally modified for the modification of gas production kinetics, e.g. by coating with or embedding in lipophilic components such as waxes or fats or suitable coatings such as polymethacrylates or polymethylmethacrylates and derivatives or similar substances known to those skilled in the art.

In another embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium or a salt thereof and a component which is expandable on contact with gastric juice to a size that precludes passage through the pylorus, and releases substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

Swelling and expanding systems are designed to be sufficiently small on administration so as not to make ingestion of a dosage form difficult. On ingestion they rapidly swell or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave the stomach.

Swelling and expanding systems that can be used for the purpose of this invention include hydrophilic erodible polymer systems. On imbibing fluid the systems swell over a short period of time to a size that will enable prolonged gastric retention, allowing controlled delivery of contained drug to absorption sites in the upper gastrointestinal tract. Because these systems are made of an erodible and hydrophilic polymer or polymer mixture, they readily erode over a reasonable time period to pass from the stomach.

In another embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium or a salt thereof and a hydrogel, wherein said composition releases substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

Hydrogels are polymers that are hydrophilic but insoluble in water. In their hydrated condition they swell to an equilibrium volume, and are elastically deformable but virtually immune to plastic deformation. In their dry state, hydrogels may be structurally rigid. The hydrogels of the expanding composition of the present invention include hydroxypropyl methylcelluloses, either alone or in combination with hydroxypropyl celluloses and/or cross-linked acrylate polymers. Suitable cross-linked acrylate polymers include polyacrylic acid crosslinked with allyl sucrose and polyacrylic acid cross linked with divinylglycol.

In another embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium or a salt thereof and at least one bioadhesive component, wherein said composition releases substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

Bioadhesive systems are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This enables gastric retention until the adhesive forces are weakened, for example by continuing hydration of the outer layer of the device or by the persistent application of shear.

A bioadhesive or mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the gastrointestinal tract (mucoadhesive polymer). Polycarbophil is a suitable polymer for encouraging adhesion of orally administered dosage forms to the gastric mucosa, thereby prolonging residence time for a system designed to slowly deliver drug to absorptive sites in the upper part of the gastrointestinal tract. Other suitable bioadhesive polymers which may be used in the present invention include chitosan, dextran sodium, poly-L-aspartic acid, polystyrene sulfonic acid, polyvinyl sulfate, polyglutamic acid, bovine serum albumin, ficoll, acidic (high isoelectric point) gelatin, polybrene, polyvinylmethyl imidazole, , polygalactosamine, proteins (polyaminoacids) such as polylysine, polyomithine, polyquaternary compounds, prolamine, polyimine, diethylaminoethyldextran (DEAE), DEAE-imine, polyvinylpyridine, polyethylene pyrrolidone, polythiodiethylaminomethylethylene (PTDAE), polyhistidine, DEAE-methacrylate, DEAE-acrylamide, poly-p-aminostyrene, polyoxethane, copolymethacrylates (eg copolymers of HPMA, N-(2-hydroxypropyl)-methacrylamide), Eudragit™ RL, Eudragit™ RS, polyamidoamines, cationic starches, DEAE-dextran and DEAE-cellulose. Chitosan can be employed as a chitosan salt (e.g., the glutamate, lactate, chloride or acetate salts) or as a chitosan derivative such as N-trimethyl chitosan chloride.

In another embodiment, the invention includes controlled release gastro-retentive pharmaceutical compositions comprising trospium or a salt thereof and at least one component that is used to provide a high density to the composition,

wherein said composition releases substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

High-density systems have a density greater than 1 g/mL, such as about 3 g/mL, are retained in the rugae of the stomach, and are capable of withstanding its peristaltic movements. Above a threshold density of about 2.4-2.8 g/mL, such systems can be retained in the lower part of the stomach.

The components that can be used to manufacture high-density formulations according to the present invention include diluents such as barium sulphate (4.9 g/mL), zinc oxide and titanium dioxide.

The invention also includes various gastro-retentive formulations like microparticles, pellets, mini-tablets, tablets and capsules to achieve gastro-retention to release substantially greater amounts of trospium into the upper part of the gastrointestinal tract.

In certain embodiments, the pharmaceutical compositions of the present invention optionally comprise pharmaceutical excipients additional to the active agent and one or more release controlling non-polymeric components, including, without limitation thereto, diluents, binders, disintegrants, surfactants, and other additives that are commonly used in solid pharmaceutical dosage form preparations.

Diluents:

Various useful fillers or diluents include but are not limited to starches, lactose, mannitol (Pearlitol™ SD200), cellulose derivatives, confectioner's sugar and the like. Different grades of lactose include but are not limited to lactose monohydrate, lactose DT (direct tableting), lactose anhydrous, Flowlac™ (available from Meggle Products), Pharmatose™ (available from DMV) and others. Different starches include but are not limited to maize starch, potato starch, rice starch, wheat starch, pregelatinized starch (commercially available as PCS PC10 from Signet Chemical Corporation) and starch 1500, starch 1500 LM grade (low moisture content grade) from Colorcon, fully pregelatinized starch (commercially available as National 78-1551 from Essex Grain Products) and others. Different cellulose compounds that can be used include crystalline cellulose and powdered cellulose. Examples of crystalline cellulose products include but are not limited to CEOLUS™ KG801, Avicel™ PH101, PH102, PH301, PH302 and PH-F20, PH-112, microcrystalline cellulose 114, and microcrystalline

cellulose 112. Other useful diluents include but are not limited to carmellose, sugar alcohols such as mannitol (Pearlitol™ SD200), sorbitol and xylitol, calcium carbonate, magnesium carbonate, dibasic calcium phosphate, and tribasic calcium phosphate.

Binders:

Various useful binders include but are not limited to hydroxypropyl celluloses, also called HPC (Klucel™ LF, Klucel EXF) and useful in various grades, hydroxypropyl methylcelluloses, also called hypromelloses or HPMC (Methocel™) and useful in various grades, polyvinylpyrrolidones or povidones (such as grades PVP-K25, PVP-K29, PVP-K30, and PVP-K90), Plasdone™ S 630 (copovidone), powdered acacia, gelatin, guar gum, carbomer (carbopol), methylcellulose, polymethacrylates, and starches.

Disintegrants:

Various useful disintegrants include but are not limited to carmellose calcium (Gotoku Yakuhin Co., Ltd.), carboxymethylstarch sodium (Matsutani Kagaku Co., Ltd., Kimura Sangyo Co., Ltd., etc.), croscarmellose sodium (Ac-di-sol™ from FMC-Asahi Chemical Industry Co., Ltd.), crospovidones, examples of commercially available crospovidone products including but not limited to crosslinked povidone, Kollidon™ CL [manufactured by BASF (Germany)], Polyplasdone™ XL, Xl-10, and INF-10 [manufactured by ISP Inc. (USA)], and low-substituted hydroxypropylcellulose. Examples of low-substituted hydroxypropylcelluloses include but are not limited to low-substituted hydroxypropylcellulose LH11, LH21, LH31, LH22, LH32, LH20, LH30, LH32 and LH33 (all manufactured by Shin-Etsu Chemical Co., Ltd.). Other useful disintegrants include sodium starch glycolate, colloidal silicon dioxide, and starches.

Surface-Active Agents:

Useful surface-active agents include non-ionic, cationic or anionic surface-active agents. Useful non-ionic surface-active agents include ethylene glycol stearates, propylene glycol stearates, diethylene glycol stearates, glycerol stearates, sorbitan esters (SPAN™) and polyhydroxyethylenically treated sorbitan esters (TWEEN™), aliphatic alcohols and PEG ethers, phenol and PEG ethers. Useful cationic surface-active agents include quaternary ammonium salts (e.g. cetyltrimethylammonium bromide) and amine salts (e.g. octadecylamine

hydrochloride). Useful anionic surface-active agents include sodium stearate, potassium stearate, ammonium stearate, and calcium stearate, triethenolamine stearate, sodium lauryl sulphate, sodium dioctylsulphosuccinate, and sodium dodecylbenzenesulphonate. Natural surface-active agents may also be used, such as for example phospholipids, e.g. diacylphosphatidyl glycerols, diaceylphosphatidyl cholines, and diaceylphosphatidic acids, the precursors and derivatives thereof, such as for example soybean lecithin and egg yolk.

Lubricants:

An effective amount of any pharmaceutically acceptable tableting lubricant can be added to assist with compressing tablets. Useful tablet lubricants include magnesium stearate, glyceryl monostearates, palmitic acid, talc, carnauba wax, calcium stearate sodium, sodium or magnesium lauryl sulfate, calcium soaps, zinc stearate, polyoxyethylene monostearates, calcium silicate, silicon dioxide, hydrogenated vegetable oils and fats, stearic acid and combinations thereof.

Glidants:

One or more glidant materials, which improve the flow of powder blends and minimize dosage form weight variations can be used. Useful glidants include but are not limited to silicone dioxide, talc and combinations thereof.

Coloring Agents:

Coloring agents can be used to color code the compositions, for example, to indicate the type and dosage of the therapeutic agent therein. Suitable coloring agents include, without limitation, natural and/or artificial compounds such as FD&C coloring agents, natural juice concentrates, pigments such as titanium oxide, iron oxides, silicon dioxide, and zinc oxide, combinations thereof, and the like.

Solvents:

Various solvents can be used in the processes of preparation of pharmaceutical compositions of the present invention including but not limited to water, methanol, ethanol, acidified ethanol, acetone, diacetone, polyols, polyethers, oils, esters, alkyl ketones, methylene chloride, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulphoxide, dimethylformamide, tetrahydrofuran and mixtures thereof.

Other additives that are useful in coatings include but are not limited to plasticizers, antiadherents, opacifiers, solvents, and optionally colorants, lubricants, pigments, antifoam agents, and polishing agents.

Various useful plasticizers include but are not limited to substances such as castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycol, propylene glycol, triacetin, and triethyl citrate. Also, mixtures of plasticizers may be utilized. The type of plasticizer depends upon the type of coating agent. An opacifier like titianium dioxide may also be present in an amount ranging from about 10% (w/w) to about 20% (w/w) based on the total weight of the coating.

Antiadhesives are frequently used in the film coating process to avoid sticking effects during film formation and drying. An example of a useful antiadhesive for this purpose is talc. The antiadhesive is frequently present in the film coating in an amount of about 5% (w/w) to 15% (w/w) based upon the total weight of the coating.

When coloured tablets are desired, the colour is frequently applied in the coating. Consequently, colouring agents and pigments may be present in a film coating. Various colouring agents include but not limited to iron oxides, which can be red, yellow, black or blends thereof.

Suitable polishing agents include polyethylene glycols of differing molecular weights and mixtures thereof, talc, surfactants (e.g. glycerol mono-stearate and poloxamers), fatty alcohols (e.g., stearyl alcohol, cetyl alcohol, lauryl alcohol and myristyl alcohol) and waxes (e.g., carnauba wax, candelilla wax and white wax). In some embodiments, polyethylene glycols having molecular weights of 3,000-20,000 are employed.

In certain embodiments, the pharmaceutical compositions of the present invention optionally include polymers as release controlling additives or as non-functional coatings include seal coating and aesthetic coating.

In embodiments, the pharmaceutical compositions of the present invention include polymers as release controlling additives either in a matrix form or in a coating form, or combinations thereof.

Polymers that can be used in the present invention include hydrophilic and hydrophobic substances, and combinations thereof. Suitable polymers include, but are not limited to, cellulose ethers, e.g., hydroxypropyl methylcelluloses or

hypromelloses (HPMC), ethylcelluloses, hydroxypropylcelluloses (HPC), hydroxyethylcelluloses and carboxymethylcellulose sodium, polyvinylpyrrolidones, including non-cross-linked polyvinylpyrrolidones, carboxymethylstarches, polyethylene glycols, polyoxyethylenes, poloxamers (polyoxyethylene-polyoxypropylene copolymers), polyvinylalcohols, glucanes (glucans), carrageenans, scleroglucanes (scleroglucans), mannans, galactomannans, gellans, alginic acid and derivatives (e.g., sodium or calcium alginate, propylene glycol alginate), polyaminoacids (e.g. gelatin), methyl vinyl ether/maleic anhydride copolymers, polysaccharides (e.g. carageenan, guar gum, xanthan gum, tragacanth and ceratonia); alpha, beta or gamma cyclodextrins, and dextrin derivatives (e.g. dextrin), polymethacrylates (e.g. copolymers of acrylic and methacrylic acid esters containing quaternary ammonium groups); cellulose esters (e.g. cellulose acetate); acrylic acid polymers (e.g. carbomers); chitosan and derivatives thereof, shellac and derivatives thereof.

Polymers that can be used in the present invention also include enteric coating polymers and combinations thereof. Suitable enteric polymers include, but are not limited to, cellulose acetate phthalates, hydroxypropyl methylcellulose phthalates, polyvinyl acetate phthalates, hydroxypropyl methylcellulose acetate succinates, cellulose acetate trimellitates, hydroxypropyl methylcellulose succinates, cellulose acetate succinates, cellulose acetate hexahydrophthalates, cellulose propionate phthalates, copolymers of methylmethacrylic acid and methyl methacrylate, copolymers of methyl acrylate, methylmethacrylate and methacrylic acid, copolymers of methylvinyl ether and maleic anhydride (Gantrez™ ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymers, natural resins such as zein, shellac and copal collophorium, carboxymethyl ethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, materials known under the trade name Eudragit® L12.5, L100, or Eudragit® S12.5, S100, and several commercially available enteric dispersion systems (e.g., Eudragit® L30D55, Eudragit® FS30D, Eudragit® L100-55, Eudragit® S100 (Evonik Industries, Germany), Kollicoat® MAE30D and 30DP (BASF), Estacryl® 30D (Eastman Chemical), Aquateric® and Aquacoat® CPD30 (FMC), and mixtures thereof.

The controlled release pharmaceutical compositions of the present invention which are in the form of capsules are usually administered to patients in

intact form and swallowed whole with a liquid such as water. For patients who have difficulty swallowing, or who are unable to, or unwilling to, swallow intact capsules, the capsules may alternatively be opened and the capsule contents sprinkled onto a small amount of soft food such as applesauce, or sprinkled into a small volume of a juice such as apple juice, and can be ingested immediately thereafter.

As used herein the term "soft food" includes, but is not limited to, applesauce, cottage cheese, ENSURE® pudding, yogurt and strained pears. Useful soft foods should be soft enough to be swallowed without chewing. As used herein the term "juice" includes, but is not limited to, apple juice, orange juice and tomato juice.

In an embodiment, a small quantity, such as about 15-20 mL, of applesauce can be placed in an empty bowl, the capsule may be carefully opened, and all of the contents inside the capsule carefully emptied onto the applesauce. The mixture can be swallowed immediately, optionally followed by drinking a glass of water to ensure complete swallowing of the contents. The contents of the capsule would not normally be chewed or crushed, and the capsule contents and applesauce mixture would not be stored for future use.

In another embodiment, approximately 60 mL of apple juice can be added to an empty bowl or glass, the capsule may be carefully opened, and all of the contents inside the capsule carefully emptied into the apple juice. Then the contents mixed briefly with the juice can be swallowed immediately. To ensure complete delivery of the dose, the bowl or glass would be rinsed with two or more volumes of juice and the contents swallowed immediately.

The bioavailability of trospium or a salt thereof, from pharmaceutical compositions of the present invention in the capsule form, will not be significantly affected when administered by sprinkling the capsule contents on soft food or juice, and will be similar to that of the intact capsules. "Bioequivalence" of two pharmaceutical products can be determined by administering the products individually to a number of subjects, and determining blood levels of a contained drug substance at intervals thereafter. The products are considered to be bioequivalent if one or more calculated bioavailability pharmacokinetic parameters are similar, i.e., have a relationship where administration of a "test" product produces pharmacokinetic parameters that are within the range of 80% to 125%

of the values obtained from administering a "reference" product. Frequently used pharmacokinetic parameters for indicating bioequivalence include:

AUC_{0-t} = Area under a plasma drug concentration versus time curve, from time zero (administration) to the last measurable concentration.

$AUC_{0-\infty}$ = Area under a plasma drug concentration versus time curve, from time zero (administration) to infinity.

C_{max} = Maximum plasma drug concentration.

T_{max} = Elapsed time from administration until the maximum measured plasma drug concentration.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof, wherein the compositions are in the form of capsules and are bioequivalent when administered, as intact capsules and as opened capsules with the contents sprinkled onto soft food or juice, to a human subject in need thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more release-controlling non-polymeric components, wherein the compositions are in the form of capsules and are bioequivalent when administered, as intact capsules and as opened capsules with the contents sprinkled onto soft food or juice, to a human subject in need thereof.

In an embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more waxes as release-controlling components, wherein the compositions are in the form of capsules and are bioequivalent when administered, as intact capsules and as opened capsules with the contents sprinkled onto soft food or juice, to a human subject in need thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or more release-controlling non-polymeric components, wherein the compositions are in the form of capsules and are bioequivalent to the commercial product SANCTURA® XR capsules, when both products are administered, by sprinkling the capsule contents onto soft food or juice, to a human subject in need thereof.

In another embodiment, the invention includes controlled release pharmaceutical compositions comprising trospium or a salt thereof and one or

more waxes as release-controlling components, wherein the compositions are in the form of capsules and are bioequivalent to the commercial product SANCTURA® XR capsules, when both products are administered, by sprinkling the capsule contents onto soft food or juice, to a human subject in need thereof.

In other embodiments, the invention includes methods of preparing pharmaceutical compositions of the present invention.

Equipment suitable for processing the pharmaceutical compositions of the present invention include rapid mixer granulators, planetary mixers, mass mixers, ribbon mixers, fluid bed processors, mechanical sifters, blenders, roller compacters, extrusion-spheronizers, compression machines, capsule filling machines, rotating bowls or coating pans; tray dryers, fluid bed dryers, rotary cone vacuum dryers, and the like, multimills, fluid energy mills, ball mills, colloid mills, roller mills, hammer mills, and the like, and different sieves. All sieves that are used for processing the pharmaceutical compositions of the present invention are sized according to the United States standard ASTM (American Standard of Testing Materials) specifications.

Dosage forms can be subjected to *in vitro* dissolution testing, such as using the procedures according to Test 711 “Dissolution” in *United States Pharmacopoeia 29*, United States Pharmacopeial Convention, Inc., Rockville, Maryland, pages 2673-2682, 2005 (“USP”) to determine the rate at which active ingredient is released from the dosage forms, and content of active substance can be determined in dissolution media using analytical techniques such as high performance liquid chromatography. The media used for dissolution testing can vary, including water, surfactant solutions, and various fluids that correspond to conditions existing in the human digestive tract. The latter fluids generally range in pH values from about 1 to about 8, and include dilute hydrochloric acid, buffers having pH values of, for example, 4.5, 5.8, and 6.8, simulated gastric fluids containing pepsin, simulated intestinal fluids containing pancreatin, etc. The compositions of numerous different media that are useful for dissolution testing are described by USP, such as the buffers on pages 3167-3168 and the gastric and intestinal fluids on page 3171.

In some embodiments, the invention includes use of packaging materials such as containers and lids of high-density polyethylene (HDPE), low-density polyethylene (LDPE) and or polypropylene and/or glass, glassine foil, aluminium

pouches, and blisters or strips composed of aluminium or high-density polypropylene, polyvinyl chloride, polyvinylidine dichloride, etc.

In further embodiments the invention includes methods of treating patients suffering from overactive bladder with symptoms of urge urinary incontinence, urgency, urinary frequency, nocturia, and urge-incontinence associated with detrusor instability, urge syndrome, and detrusor hyperreflexia using the pharmaceutical compositions of the present invention.

The pharmaceutical dosage forms of the present invention are intended for oral administration to a patient in need thereof.

Certain specific aspects and embodiments of the invention will be explained in more detail with reference to the following examples, being provided only for purposes of illustration, and it is to be understood that the present invention is not to be limited thereto.

EXAMPLES 1-4: Trospium chloride 60 mg controlled release capsules (wax based mini-tablets filled into hard gelatin capsules, drug to wax ratio 1:3).

Ingredient	Grams			
	Example 1	Example 2	Example 3	Example 4
Trospium chloride	2	2	2	2
Stearic acid	6	-	6	-
Hydrogenated castor oil	-	6	-	-
Glyceryl behenate	-	-	-	6
Microcrystalline cellulose (Avicel™ PH102)*	1.85	1.85	1.85	1.85
Colloidal silicon dioxide	0.05	0.05	0.05	0.05
Talc	0.05	0.05	0.05	0.05
Magnesium stearate	0.05	0.05	0.05	0.05

* Avicel PH102 is supplied by FMC Biopolymer.

Example 1 manufacturing process:

1) Stearic acid was melted to form a clear liquid.

2) Trospium chloride was added to the liquid of step 1) with constant stirring.

3) Half of the microcrystalline cellulose was added to the molten dispersion of step 2) and remaining microcrystalline cellulose was added with stirring when the wax started solidifying while being brought to room temperature.

4) The solidified mixture of step 3) was passed through a #40 mesh sieve.

5) Colloidal silicon dioxide, talc and magnesium stearate were added to the blend of step 4) and mixed thoroughly.

6) The blend of step 5) was compressed into mini-tablets, each weighing 10 mg, using 2.5 mm round, deep concave punches.

7) Mini-tablets of step 6) equivalent to 60 mg of trospium chloride were filled into size '0' elongated hard gelatin capsules.

Example 2 manufacturing process was similar to that described in Example 1, except that hydrogenated castor oil was used instead of stearic acid.

Example 3 manufacturing process:

1) Stearic acid was melted to form a clear liquid.

2) Trospium chloride was added to the liquid of step 1) with constant stirring.

3) The mixture of step 2) was brought to room temperature with constant stirring until it solidified.

4) The solidified mixture of step 3) was passed through a #30 mesh sieve.

5) Microcrystalline cellulose was added to the mixture of step 4) and blended thoroughly, then the mixture was passed through a #40 mesh sieve.

6) Colloidal silicon dioxide, talc and magnesium stearate were added to the blend of step 5) and mixed thoroughly.

7) The blend of step 6) was compressed into mini-tablets, each weighing 10 mg, using 2.5 mm round, deep concave punches.

8) Mini-tablets of step 7) equivalent to 60 mg of trospium chloride were filled into size '0' elongated hard gelatin capsules.

Example 4 manufacturing process was similar to that described in Example 3, except that glyceryl behenate was used instead of stearic acid.

Trospium chloride 60 mg controlled release capsules of the above examples were analyzed to determine the drug assay (expressed as a percentage

of the theoretical drug content) and *in vitro* dissolution profiles, and the results are given below.

Assay Results

Example 1	Example 2	Example 3	Example 4
95.5	101.5	97.8	105.3

In vitro dissolution testing was conducted according to the USP procedure, with the following conditions:

Apparatus: USP type II.

Stirring speed: 50 rpm.

Dissolution medium: pH 6.8 phosphate buffer.

Volume of dissolution medium: 950 ml.

Dissolution Results

Time (hours)	Cumulative % of Drug Dissolved			
	Example 1	Example 2	Example 3	Example 4
1	32.3	44.3	74	47
2	47.7	62.3	86.7	71
4	62.7	85	97.3	98.3
6	71	95.7	99.7	106
8	76.3	99.7	100	108
12	84.7	100.3	101	109.3

EXAMPLES 5-6: Trospium chloride 60 mg controlled release capsules (tablet based on combination of waxes filled into hard gelatin capsule).

Ingredient	Grams	
	Example 5	Example 6
Trospium chloride	2	2
Stearic acid	3	3
Hydrogenated castor oil	3	-
Glyceryl behenate	-	3
Microcrystalline cellulose (Avicel PH102)	1.85	1.85
Colloidal silicon dioxide	0.05	0.05

Talc	0.05	0.05
Magnesium stearate	0.05	0.05

Example 5 manufacturing process:

1) Stearic acid and hydrogenated castor oil were melted to form a clear liquid.

2) Trospium chloride was added to the liquid of step 1) with constant stirring.

3) Half of the microcrystalline cellulose was added to the molten dispersion of step 2) and remaining microcrystalline cellulose was added with stirring when the wax started solidifying as it was brought to room temperature

4) The solidified mixture of step 3) was passed through a #40 mesh sieve.

5) Colloidal silicon dioxide, talc and magnesium stearate were added to the blend of step 4) and mixed thoroughly.

6) The blend of step 5) equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine and filled into size '0' elongated hard gelatin capsules.

Example 6 manufacturing process was the same as that described in Example 5, except that glyceryl behenate was used instead of hydrogenated castor oil.

EXAMPLES 7-8: Trospium chloride 60 mg controlled release capsules (wax based spheres filled into hard gelatin capsules).

Ingredient	**Grams**	
	Example 7	**Example 8**
Trospium chloride	60	60
Sugar spheres*	225	225
Stearic acid	60	-
Carnauba wax	-	60
Triethyl citrate	5	3
Talc	-	2
Isopropyl alcohol‡	200	200

* Sugar spheres of sizes 800-1200 µm, supplied by NP Pharm.

‡ Evaporates during processing.

Example 7 manufacturing process:

1) Stearic acid was dissolved in isopropyl alcohol.

2) Trospium chloride was added to the solution of step 1) with stirring.

3) Triethyl citrate was added with stirring to the dispersion of step 2)

4) Sugar spheres were placed in a fluidized bed coater and coated with the dispersion of step 3). Inside temperature of the fluidized bed coater was maintained at about 30 to 35ºC to solidify stearic acid during the coating process.

5) Coated spheres equivalent to 60 mg of trospium chloride were filled into size '0' elongated hard gelatin capsules.

Example 8 manufacturing process:

1) Carnauba wax was dissolved in isopropyl alcohol.

2) Trospium chloride was added to the solution of step 1) with stirring.

3) Triethyl citrate and talc were added with stirring to the dispersion of step 2)

4) Sugar spheres were placed in a fluidized bed coater and coated with the dispersion of step 3). Inside temperature of the fluidized bed coater was maintained at about 30 to 35ºC to solidify carnauba wax during the coating process.

5) Coated spheres equivalent to 60 mg of trospium chloride were filled into size '0' elongated hard gelatin capsules.

EXAMPLES 9-11: Trospium chloride 60 mg controlled release capsules (resinate tablets filled into hard gelatin capsules).

Ingredient	**Grams**		
	Example 9	**Example 10**	**Example 11**
Trospium chloride	2	2	2
Amberlite™ IRP 69*	6	-	-
Amberlite IRP 67*	-	6	-
Amberlite IRC 748*	-	-	6
Microcrystalline cellulose (Avicel PH102)	1.85	1.85	1.85
Colloidal silicon dioxide	0.05	0.05	0.05

Talc	0.05	0.05	0.05
Magnesium stearate	0.05	0.05	0.05
Water‡	10	10	10

* Amberlite products are supplied by Rohm and Hass.

‡ Evaporates during processing.

Example 9 manufacturing process:

1) Amberlite IRP 69 was dispersed in water.

2) Trospium chloride was added to the dispersion of step 1).

3) The dispersion of step 2) was stirred for 5 hours to ensure complex formation.

4) The supernatant of the dispersion of step 3) was separated and dried at 60ºC.

5) Microcrystalline cellulose was added to the dried resinate of step 4) and blended thoroughly.

6) Colloidal silicon dioxide, talc and magnesium stearate were added to the blend of step 5) and mixed thoroughly.

7) The blend of step 6) equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine and filled into size '0' elongated hard gelatin capsules.

Example 10 manufacturing process was the same as that described in Example 9, except that Amberlite IRP 67 was used instead of Amberlite IRP 69.

Example 11 manufacturing process was the same as that described in Example 9, except that Amberlite IRC 748 was used instead of Amberlite IRP 69.

EXAMPLES 12-13: Trospium chloride 60 mg controlled release capsules (wax and resin based tablets filled into hard gelatin capsules)

Ingredient	**Grams**	
	Example 12	**Example 13**
Trospium chloride	2	2
Amberlite IRP 69	2	2
Stearic acid	4	-
Glyceryl behenate	-	4
Microcrystalline cellulose	1.85	1.85

(Avicel PH102)		
Colloidal silicon dioxide	0.05	0.05
Talc	0.05	0.05
Magnesium stearate	0.05	0.05
Water‡	10	10

‡ Evaporates during processing.

Example 12 manufacturing process:

1) Stearic acid was melted to form a clear liquid.

2) Trospium chloride resin complex with Amberlite IRP 69 was prepared according to Example 9 (steps 1-4).

3) The prepared drug resinate of step 2) was added to the molten wax of step 1) and mixed thoroughly.

4) Half of the microcrystalline cellulose was added to the dispersion of step 3) and remaining microcrystalline cellulose was added with stirring when the wax started solidifying as it was brought to room temperature.

5) The solidified mixture of step 4) was passed through a #40 mesh sieve.

6) Colloidal silicon dioxide, talc and magnesium stearate were added to the blend of step 5) and mixed thoroughly.

7) The blend of step 6) equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine and filled into size '0' elongated hard gelatin capsules.

Example 13 manufacturing process was the same as that described in Example 12, except that glyceryl behenate was used instead of stearic acid.

EXAMPLE 14: Trospium chloride 60 mg controlled release capsules (osmotic coated tablets filled into hard gelatin capsules).

Ingredient	Grams
Trospium chloride	2
Stearic acid	6
Microcrystalline cellulose (Avicel PH102)	1.85
Colloidal silicon dioxide	0.05
Talc	0.05

Magnesium stearate	0.05
Coating	
Cellulose acetate	0.95
Triethyl citrate	0.05
Acetone‡	50

‡ Evaporates during processing.

Manufacturing process:

1) Stearic acid was melted to form a clear liquid.

2) Trospium chloride was added to the liquid of step 1) with constant stirring.

3) Half of the microcrystalline cellulose was added to the molten dispersion of step 2) and remaining microcrystalline cellulose was added with stirring as the wax started solidifying while being brought to room temperature.

4) The solidified mixture of step 3) was passed through a #40 mesh sieve.

5) Colloidal silicon dioxide, talc and magnesium stearate were added to the blend of step 4) and mixed thoroughly.

6) The blend of step 5) equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine.

7) Cellulose acetate was dissolved in acetone.

8) Triethyl citrate was added to the solution of step 7) and stirred to dissolve.

9) The tablets of step 6) were coated with coating solution of step 8).

10) The coated tablets of step 9) were drilled on one edge of each tablet with a 0.6 mm mechanical drill and filled into size '0' elongated hard gelatin capsules.

EXAMPLES 15-17: Trospium chloride 60 mg controlled release tablets.

Ingredient	**mg/Tablet**		
	Example 15	**Example 16**	**Example 17**
Trospium chloride	60	60	60
Stearic acid	55	-	-
Hydrogenated castor oil	65	90	54

Hydroxypropyl methylcellulose (Methocel™ K15M)*	-	58	-
Eudragit™ L 100**	-	-	15
Microcrystalline cellulose (Avicel PH 102)	77	-	132
Dicalcium phsophate	-	58.5	-
Lactose monohydrate	38.5	29	34.5
Colloidal silicon dioxide	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5
Coating			
Eudragit L 100	13.5	-	18.69
Triethyl citrate	1.5	-	2.1
Talc	-		0.21
Acetone‡	0.125	-	-
Isopropyl alcohol‡	0.375	-	0.525
Water‡	-	-	0.131

* Methocel K15M is supplied by Dow Chemical Company.

** Eudragit products are supplied by Evonik Industries, Germany.

‡ Evaporates during processing.

Example 15 manufacturing process:

1. Trospium chloride, stearic acid and hydrogenated castor oil were weighed, passed through a #40 mesh sieve and blended thoroughly.

2. Microcrystalline cellulose and lactose were added to the blend of step 1 and mixed thoroughly.

3. Colloidal silicon dioxide was passed through a #40 mesh sieve, added to the blend of step 2 and mixed thoroughly.

4. Talc and magnesium stearate were passed through a #60 mesh sieve, added to the blend of step 3 and mixed thoroughly.

5. The blend of step 4 equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine.

6. Eudragit L 100 and triethyl citrate were dissolved in a mixture of acetone and isopropyl alcohol.

7. The tablets of step 5 were coated with coating solution of step 6.

Example 16 manufacturing process:

1. Trospium chloride, hydroxypropyl methylcellulose and hydrogenated castor oil were weighed, passed through a #40 mesh sieve and blended thoroughly.

2. Dicalcium phosphate and lactose were added to the blend of step 1 and mixed thoroughly.

3. Colloidal silicon dioxide was passed through a #40 mesh sieve, added to the blend of step 2 and mixed thoroughly.

4. Talc and magnesium stearate were passed through a #60 mesh sieve, added to the blend of step 3 and mixed thoroughly.

5. The blend of step 4 equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine.

Example 17 manufacturing process:

1. Trospium chloride, Eudragit L 100 and hydrogenated castor oil were weighed, passed through a #40 mesh sieve and blended thoroughly.

2. Microcrystalline cellulose and lactose were added to the blend of step 1 and mixed thoroughly.

3. Colloidal silicon dioxide was passed through a #40 mesh sieve, added to the blend of step 2 and mixed thoroughly.

4. Talc and magnesium stearate were passed through a #60 mesh sieve, added to the blend of step 3 and mixed thoroughly.

5. The blend of step 4 equivalent to 60 mg of trospium chloride was compressed into tablets using a 16 station compression machine.

6. Eudragit L 100 and triethyl citrate were dissolved in a mixture of isopropyl alcohol and water.

7. Talc was added to the solution of step 6 and stirred for 20 minutes.

8. The tablets of step 5 were coated with coating of step 7.

Trospium chloride 60 mg controlled release tablets of the above examples were analyzed to determine their *in vitro* dissolution profiles, and compared with the dissolution profile of a commercial reference product, SANCTURA® XR 60 mg extended release capsules from Indevus Pharmaceuticals, Batch No. 0702997, obtained from the USA.

In vitro dissolution testing conditions:

Apparatus: USP type II.

Stirring speed: 50 rpm.

Dissolution media: 750 ml of 0.1N HCl for the initial 2 hours, and then 950 ml of pH 7.5 phosphate buffer.

Dissolution Results

Time (hours)	Cumulative % of Drug Dissolved		
	SANCTURA	Example 15	Example 17
1	10.5	11	0
2	21	27.3	2.2
2.5	63.5	45	15.2
3	73	53.7	26
4	77	64.7	43.5
8	88	82.7	83.3
12	92.5	89.7	95.7
16	94.5	95	99.8

EXAMPLE 18: Trospium chloride 60 mg controlled release tablets.

Ingredient	mg/Tablet
Trospium chloride	60
Stearic acid	55
Hydrogenated castor oil	65
Microcrystalline cellulose (Avicel PH 102)	77
Lactose monohydrate	38.5
Colloidal silicon dioxide	1.5
Talc	1.5
Magnesium stearate	1.5
Dichloromethane‡	q.s.
Methanol‡	q.s.

‡ Evaporates during processing.

Manufacturing process:

1. Prepare a solvent mixture of dichloromethane and methanol.

2. Add trospium chloride, stearic acid and hydrogenated castor oil to the solvent mixture of step 1 and dissolve them with slight heating of solution at a temperature of about 35 to 40°C.

3. Add lactose to microcrystalline cellulose and blend thoroughly.

4. Spray the solution of step 2 onto the blend of step 3.

5. Pass the granulation blend of step 4 through a #40 mesh sieve.

6. Add colloidal silicon dioxide, talc and magnesium stearate to the granules of step 5 and blend thoroughly.

7. Compress the blend of step 6 equivalent to 60 mg of trospium chloride into tablets.

EXAMPLES 19-21: Trospium chloride 60 mg controlled release capsules (two tablets filled into a capsule).

Ingredient	**mg/Capsule**		
	Example 19	**Example 20**	**Example 21**
Tablet 1			
Trospium chloride	12	12	24
Hydrogenated castor oil	15	15	30
Microcrystalline cellulose (Avicel PH 102)	42	42	30
Lactose monohydrate	29	29	14
Colloidal silicon dioxide	1	1	1
Magnesium stearate	1	1	1
Total	100	100	100
Tablet 2			
Trospium chloride	48	48	36
Hydrogenated castor oil	72	105	105
Microcrystalline cellulose (Avicel PH 102)	75	60	65
Lactose monohydrate	50	32	39
Colloidal silicon dioxide	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5
Eudragit L 100	16	16	16

Talc	2.4	2.4	2.4
Triethyl citrate	1.6	1.6	1.6
Isopropyl alcohol‡	0.14	0.14	0.14
Water‡	0.03	0.03	0.03

‡ Evaporates during processing.

Example 19 manufacturing process:

Tablet 1:

1. Trospium chloride and hydrogenated castor oil were weighed and passed through a #40 mesh sieve and blended thoroughly.

2. Microcrystalline cellulose and lactose were added to the blend of step 1 and mixed thoroughly.

3. Colloidal silicon dioxide was passed through a #40 mesh sieve, added to the blend of step 2 and mixed thoroughly.

4. Magnesium stearate was passed through a #60 mesh sieve, added to the blend of step 3 and mixed thoroughly.

5. The blend of step 4 equivalent to 12 mg of trospium chloride was compressed into tablets using 5 mm round shaped punches on a 16 station compression machine.

Tablet 2:

1. Trospium chloride and hydrogenated castor oil were weighed, passed through a #40 mesh sieve and blended thoroughly.

2. Microcrystalline cellulose and lactose were added to the blend of step 1 and mixed thoroughly.

3. Colloidal silicon dioxide was passed through a #40 mesh sieve, added to the blend of step 2 and mixed thoroughly.

4. Magnesium stearate was passed through a #60 mesh sieve, added to the blend of step 3 and mixed thoroughly.

5. The blend of step 4 equivalent to 48 mg of trospium chloride was compressed into tablets using 12×5 mm capsule shaped punches on a 16 station compression machine.

6. Eudragit L 100 and triethyl citrate were dissolved in a mixture of isopropyl alcohol and water.

7. Talc was added to the solution of step 6 and stirred for 20 minutes.

8. The tablets of step 5 were coated with coating of step 7.

Finally, one each of Tablet 1 and Tablet 2 were filled into a size '1' hard gelatin capsule.

Examples 20 and 21 manufacturing processes were similar to the process described in Example 19.

Trospium chloride 60 mg controlled release capsules of the above examples were tested to determine their *in vitro* dissolution profiles using the following conditions:

Apparatus: USP type III.

Dips per minute: 10.

Dissolution media: 0.1N HCl for the first hour, pH 4.5 acetate buffer for the second hour, pH 5.5 phosphate buffer for the third hour, pH 6.5 phosphate buffer for hours 3-6, and pH 7.5 phosphate buffer for hours 6-8.

Volume of dissolution medium: 250 ml.

Dissolution Results

Time (hours)	**Cumulative % of Drug Dissolved**		
	Example 19	**Example 20**	**Example 21**
1	14	13	21
2	21	21	32
3	27	27	39
4	35	39	44
6	59	74	64
8	76	92	78

EXAMPLES 22-25: Trospium chloride 60 mg controlled release capsules (two different mini-tablets filled into a capsule).

Ingredient	**mg/Capsule**			
	Example 22	**Example 23**	**Example 24**	**Example 25**
Mini-tablets 1				
Trospium chloride	12	18	24	30
Hydrogenated castor oil	60	60	70	72.12
Dichloromethane‡	36	39	47	51

Microcrystalline cellulose (Avicel PH102)	30	30	14	16.46
Lactose monohydrate	16.58	10.58	10.58	-
Colloidal silicon dioxide	1.21	1.21	1.21	1.21
Magnesium stearate	1.21	1.21	1.21	1.21
Mini-tablets 2				
Trospium chloride	48	42	36	30
Hydrogenated castor oil	60	55	50	48
Dichloromethane‡	54	49	43	39
Microcrystalline cellulose (Avicel PH102)	10.58	11	20	27
Lactose monohydrate	-	10.58	12.58	13.46
Colloidal silicon dioxide	1.21	1.21	1.21	1.21
Magnesium stearate	1.21	1.21	1.21	1.21
Eudragit L 100	51.7	37.96	29.04	19.2
Talc	0.6	5.69	4.4	3
Triethyl citrate	6	3.79	2.86	2
Polyethylene glycol 6000	-	0.95	-	-
Isopropyl alcohol‡	0.71	0.71	0.44	0.36
Water‡	0.14	0.14	0.09	0.07

‡ Evaporates during processing.

Manufacturing process:

Mini-tablets 1:

1. Trospium chloride and hydrogenated castor oil were passed through a #40 mesh sieve and blended thoroughly.

2. Blend of step 1 was loaded into a rapid mixer granulator and granulated with dichloromethane.

3. Granules were dried in fluidized bed dryer at 45°C for 15 to 20 minutes.

4. Dried granules were sifted through #30 mesh sieve. Retained particles were milled through a multimill equipped with a 1.5 mm screen, passed through a #30 mesh sieve, and combined with sifted granules.

5. Microcrystalline cellulose, lactose (if used) and colloidal silicon dioxide were added to the granules of step 4 after passing through a #40 mesh sieve and mixed thoroughly in a double cone blender for 10 minutes.

6. Magnesium stearate was passed through a #60 mesh sieve, added to the blend of step 5 and blended for 5 minutes.

5. The blend of step 6 was compressed into mini-tablets, each weighing 11 mg, using 2.5 mm standard, concave multi-tip punches on a 16 station compression machine.

Mini-tablets 2:

1. Trospium chloride and hydrogenated castor oil were passed through a #40 mesh sieve.

2. Blend of step 1 was loaded into a rapid mixer granulator and granulated with dichloromethane.

3. Granules were dried in a fluidized bed drier at 45°C for 15 to 20 minutes.

4. Dried granules were sifted through a #30 mesh sieve. Retained particles were milled through a multimill equipped with a 1.5 mm screen, passed through a #30 mesh sieve, and combined with sifted granules.

5. Microcrystalline cellulose, lactose (if used) and colloidal silicon dioxide were added to the granules of step 4 after passing through a #40 mesh sieve, and mixed thoroughly in a double cone blender for 10 minutes.

6. Magnesium stearate was passed through a #60 mesh sieve, added to the blend of step 5 and blended for 5 minutes.

7. The blend of step 6 was compressed into mini-tablets, each weighing 11 mg, using 2.5 mm standard, concave multi-tip punches on a 16 station compression machine.

8. Eudragit L 100 was dissolved in a mixture of isopropyl alcohol and water (80:20 by volume).

9. Talc and polyethylene glycol 6000 (if used) were added to the solution of step 8 and homogenized for 20 minutes.

10. Triethyl citrate was added to the dispersion of step 9 and stirred for 45 minutes.

11. The mini-tablets of step 7 were coated with coating solution of step 10.

12. Finally, a mini-tablet 1 and a mini-tablet 2 were filled into a size '1' hard gelatin capsule.

Trospium chloride 60 mg controlled release capsules of Example 25 were tested to determine their *in vitro* dissolution profiles using the following conditions:

Apparatus: USP type II.

Rpm: 50.

Dissolution media: 750 ml of 0.1N HCl for the first 2 hours, then 950 ml of pH 6.0 phosphate buffer.

Dissolution Results

Time (hours)	**Cumulative % of Drug Dissolved**
0.5	0
1	18
2	26
2.5	48
4	53
6	63

EXAMPLE 26: Trospium chloride 60 mg controlled release capsules (multiparticulates filled into capsules).

Ingredient	**mg/Capsule**
Drug-layered Pellets	
Celphere™ *	160
Trospium chloride	60
Hydroxypropyl methylcellulose 5 cps	6
Dichloromethane‡	0.74
Methanol‡	0.74
Delayed Release (DR) Pellets	
Drug layered pellets	113
Eudragit L 100	24
Triethyl citrate	3
Acetone‡	1.07

Isopropyl alcohol‡	2.14
Controlled Release (CR) Pellets	
Drug layered pellets	113
Stearic acid	35
Hydrogenated castor oil	30
Triethyl citrate	5.5
Dichloromethane‡	3.48
Methanol‡	1.72

* Celphere is microcrystalline cellulose spherical seed cores manufactured by Asahi Kasei in Japan.

‡ Evaporates during processing.

Manufacturing process:

Drug-layered pellets:

1. Load the Celphere pellets into a fluid bed processor.
2. Dissolve trospium chloride and hydroxypropyl methylcellulose in a mixture of dichloromethane and methanol.
3. Spray the solution of step 2 onto the pellets of step 1 with subsequent drying for drug loading. After drug loading, divide the pellets into two halves for DR and CR coating.

DR pellets:

1. Load drug-layered pellets into fluid bed processor.
2. Prepare a coating solution by dissolving Eudragit L 100 and triethyl citrate in a mixture of acetone and Isopropyl alcohol.
3. Spray the coating solution of step 2 onto the drug-layered pellets of step 1.
4. Cure the coated pellets of step 3 for 30 minutes in the fluid bed processor.

CR pellets:

1. Load drug-layered pellets into fluid bed processor.
2. Prepare a coating solution by dissolving hydrogenated castor oil, stearic acid and triethyl citrate in a mixture of dichloromethane and methanol.
3. Spray the coating solution of step 2 onto the drug-layered pellets of step 1.

4. Cure the coated pellets of step 3 for 30 minutes in the fluid bed processor.

Finally, fill DR pellets equivalent to 30 mg of trospium chloride and CR pellets equivalent to 30 mg of trospium chloride into size '1' hard gelatin capsules.

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CLAIMS:

1. A pharmaceutical formulation comprising trospium or a salt thereof and at least one of a wax material and an ion exchange resin, releasing less than about 90 percent of contained trospium within about 6 hours after immersion into an aqueous fluid.

2. The pharmaceutical formulation of claim 1, wherein trospium is present in a wax material-containing matrix.

3. The pharmaceutical formulation of claim 1, wherein trospium is present in a core having a wax material-containing coating.

4. The pharmaceutical formulation of any of claims 1-3, comprising about 30 to about 80 percent by weight of one or more wax materials.

5. The pharmaceutical formulation of claim 1, wherein trospium is complexed with an ion exchange resin.

6. The pharmaceutical formulation of any of claims 1-5, comprising two or more formulated fractions having different trospium release profiles.

7. The pharmaceutical formulation of claim 6, wherein a formulated fraction is a mini-tablet.

8. The pharmaceutical formulation of claim 6, wherein a formulated fraction is in the form of a powder, granules, beads, or pellets.

9. The pharmaceutical formulation of claim 6, wherein a formulated fraction comprises trospium present in a wax material-containing matrix, and another formulated fraction comprises trospium complexed with an ion exchange resin.

10. The pharmaceutical formulation of any of claims 1-9, further including an outer coating comprising an enteric polymer.

11. The pharmaceutical formulation of any of claims 1-10, comprising two or more mini-tablets, having different trospium release profiles, filled into a capsule.

12. The pharmaceutical formulation of any of claims 1-11, releasing at least about 10 percent of contained trospium into a lower part of the gastrointestinal tract.

13. A process for preparing a pharmaceutical formulation, comprising combining trospium or a salt thereof with a wax material or an ion exchange resin to obtain a formulation that releases less than about 90 percent of contained trospium within about 6 hours after immersion into an aqueous fluid.

14. The process of claim 13, comprising forming a matrix composition comprising trospium or a salt thereof and a wax material.

15. The process of claim 13, comprising forming a coating including a wax material over a core including trospium or a salt thereof.

16. The process of claim 13, comprising forming a complex from trospium, or a salt thereof, and an ion exchange resin.

17. The process of any of claims 13-16, further comprising forming an outer coating comprising an enteric polymer.

18. The process of any of claims 13-17, wherein a pharmaceutical formulation comprises at least two different formulated components.

19. The process of claim 18, wherein a pharmaceutical formulation comprises at least one mini-tablet comprising trospium or a salt thereof and one or more pharmaceutical excipients.

20. The process of claim 18, wherein a pharmaceutical formulation comprises at least one granulated composition comprising trospium or a salt thereof and one or more pharmaceutical excipients.

21. The process of claim 18, wherein a pharmaceutical formulation comprises at least one bead or pellet composition comprising trospium or a salt thereof and one or more pharmaceutical excipients.