PHARMACEUTICAL FORMULATIONS FOR THE TREATMENT OF OVERACTIVE BLADDER

RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Application No. 61/320,202, filed April 1, 2010, by Mehdi Paborji, and entitled "PHARMACEUTICAL FORMULATIONS FOR THE TREATMENT OF OVERACTIVE BLADDER," which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[002] The present invention is in the field of pharmaceutical formulations, and in particular formulations comprising pilocarpine or cevimeline, formulations comprising a muscarinic antagonist, and formulations comprising a combination of pilocarpine or cevimeline and a muscarinic antagonist.

BACKGROUND OF THE DISCLOSURE

[003] Muscarinic receptor antagonists, such as tolterodine, are known for the treatment of overactive bladder. However, an adverse side effect of these treatments is severe dry mouth. This side effect causes significant patient discomfort and reduces compliance greatly. Previous work has shown that the combination of tolterodine or oxybutynin with pilocarpine, a muscarinic receptor agonist that increases saliva formation, can significantly reduce the incidents of dry mouth while not affecting the efficacy of the muscarinic receptor antagonist. See, for example, U.S. Patent Nos. 7,666,894, 7,678,821, and 7,781,472, and U.S. Application Publication Nos. 2009/0275629 and 2010/0152263, all of which are incorporated herein by reference in their entirety.

[004] As discussed in the aforementioned publications, one cannot simply take a muscarinic antagonist and pilocarpine or cevimeline and expect to obtain the desired clinical efficacy. The timing of the administration of the muscarinic agonist vis-à-vis the administration of the muscarinic antagonist has to be adjusted properly so that the maximum increase in saliva formation due to the administration of the muscarinic agonist is reached at the same time as the maximum dry mouth experienced due to the administration of the muscarinic antagonist. Taking

two tablets at two different times, where the time difference between the two administrations has to be exact, is inconvenient, cumbersome, and reduces patient compliance. Therefore, a single pharmaceutical formulation is needed where the desired time delay and release profile are incorporated.

SUMMARY OF THE INVENTION

[005] Disclosed herein are pharmaceutical compositions comprising a plurality of first beads each comprising: a core; a first layer comprising pilocarpine, cevimeline, or a pharmaceutically acceptable salt thereof; and a second layer comprising a first polymer. Also disclosed are pharmaceutical compositions comprising a plurality of second beads each comprising: a core; and a first layer comprising a muscarinic antagonist or a pharmaceutically acceptable salt thereof. Further disclosed are pharmaceutical formulations comprising: a) a plurality of the first beads; b) a plurality of the second beads; or c) a plurality of the first beads and a plurality of the second beads.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[006] Aspects of the present disclosure include pharmaceutical formulations comprising a muscarinic antagonist in an immediate release formulation. Once ingested by a subject, the muscarinic antagonist in these formulations begins to release into the gut to be systemically absorbed into the blood stream. Other aspects of the present disclosure include pharmaceutical formulations comprising pilocarpine or cevimeline, both of which are muscarinic agonists. The muscarinic agonist of the pharmaceutical formulations is present in a delayed immediate release formulation. Once ingested, the muscarinic agonist is not released for some time. But once the muscarinic agonist begins to be released, it is released immediately.

[007] In some embodiments, the muscarinic antagonist of the formulations disclosed herein is a compound that is used for the treatment of overactive bladder. In certain embodiments, the muscarinic antagonist is selected from the group consisting of tolterodine, 5-hydroxymethyl tolterodine, fesoterodine, oxybutynin, solifenacin, darifenacin, trospium, imidafenacin, propiverine, and dicyclomine.

[008] In the context of the present disclosure, "immediate release" or "released immediately" means that at least about 70% of the ingested active

pharmaceutical ingredient in the dosage form is released from the pharmaceutical formulation within about 30-60 minutes of the ingestion of the dosage form. By "not released" or "delayed released" it is meant that less than 20% of the ingested active pharmaceutical ingredient in the dosage form is released from the pharmaceutical formulation by the time the delay is concluded and the release becomes immediate.

[009] Throughout the present disclosure the term "about" a certain value means that a range of value±10%, and preferably a range of value±5%, is contemplated. Thus, for example, having about 70% of the active pharmaceutical ingredient (API) includes API being present between 63% and 87%, and preferably between 66.5% and 73.5%; or by way of another example, "about 45 minutes" means that the contemplated value is between 40.5 minutes and 49.5 minutes, and preferably between 42.75 minutes and 47.25 minutes.

[0010] Disclosed herein are beads, or multiparticulate systems, comprising a muscarinic agonist, i.e., pilocarpine or cemiveline, and other beads comprising a muscarinic antagonist. Contemplated within the scope of the present disclosure are pharmaceutical compositions comprising muscarinic agonist beads only, muscarinic antagonist beads only, or compositions comprising both muscarinic agonist and muscarinic antagonist beads. The muscarinic agonist-only or muscarinic antagonist-only beads can be administered individually or in combination with beads or other pharmaceutical formulations comprising other active ingredients.

MUSCARINIC AGONIST BEADS

[0011] Thus, in one aspect, disclosed herein are pharmaceutical compositions comprising a plurality of first beads each comprising:

a core;

a first layer comprising a muscarinic agonist, i.e., pilocarpine or cemiveline, or a pharmaceutically acceptable salt thereof; and

a second layer comprising a first polymer.

[0012] In some embodiments, the core comprises a polymer. In certain embodiments, the core polymer is a cellulose polymer. In some of these embodiments, the cellulose polymer is microcrystalline cellulose. In other embodiments, the core comprises a sugar. In certain embodiments, the sugar is selected from the group consisting of glucose, sucrose, lactose, mannitol,

maltodextrine, xylitol, and sorbitol. In further embodiments, the core comprises silicon dioxide.

[0013] In some embodiments, the core is obtained commercially. An example of commercially available beads to be used as core for the beads disclosed herein includes, but is not limited to, sugar spheres (for example, Paular spheres), Cellets® cores, such as Cellets® 100, Cellets® 200, Cellets® 350, Cellets® 500, Cellets® 700, or Cellets® 1000 (Glatt Air Techniques Inc., Ramsey NJ). In other embodiments, the core is prepared de novo, for example by preparing a polymer mixture, extruding the mixture, and spheronizing the extruded mixture to form spherical or semi-spherical beads. In some embodiments, the beads are swellable such that their exposure to aqueous media causes them to swell and release the active ingredient rapidly and efficiently.

[0014] In some embodiments, the core comprises between about 10% to about 50% of the total weight of the finally-formulated bead. In some embodiments, the core comprises between about 15% to about 40% of the total weight of the finally-formulated bead. In some embodiments, the core comprises between about 20% to about 30% of the total weight of the finally-formulated bead. In some embodiments, the core comprises about 20% of the total weight of the finally-formulated bead. In some embodiments, the core comprises about 25% of the total weight of the finally-formulated bead.

[0015] In some embodiments, a solution of the muscarinic agonist, a free base thereof or a pharmaceutically acceptable salt thereof, is prepared and then sprayed onto the core and then dried. The act of spraying and drying causes a layer (the first layer) of the API (i.e., pilocarpine or cevimeline) to form over the bead. In some embodiments, the solution comprises a polymer that causes the API to more efficiently adhere to the core. The amount of the API present in the dosage form can be controlled by controlling the thickness of the first layer and/or by the concentration of the solution comprising the API. The thicker the first layer, or the more concentrated the API solution, the more API is present in the dosage form. Once the first layer is exposed to aqueous media, for example gastric or intestinal juice, the pilocarpine contained therein immediately dissolves into the aqueous medium. Methods of applying the first layer uniformly onto the core are well-known in the art.

[0016] In some embodiments, the first layer comprises between about 1% to about 50% of the total weight of the bead. In some embodiments, the first layer

comprises between about 2% to about 40% of the total weight of the bead. In some embodiments, the first layer comprises between about 5% to about 30% of the total weight of the bead. In some embodiments, the first layer comprises between about 7% to about 25% of the total weight of the bead. In some embodiments, the first layer comprises between about 8% to about 15% of the total weight of the bead. In some embodiments, the first layer comprises about 8% of the total weight of the bead. In some embodiments, the first layer comprises about 10% of the total weight of the bead. In some embodiments, the first layer comprises about 12% of the total weight of the bead. In some embodiments, the first layer comprises about 15% of the total weight of the bead.

[0017] In some embodiments, pilocarpine or cevimeline is present as the free base. In other embodiments, pilocarpine or cevimeline is present as a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as tartric acid, oxolic acid, "carbonic acid" to form the bicarbonate or carbonate salt of the compound, acetic acid, formic acid, benzoic acid, and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like. In some embodiments, the pilocarpine is pilocarpine HCl or pilocarpine nitrate.

[0018] Once the API (pilocarpine, cevimeline, or a salt thereof) is coated onto the bead, the bead is coated with a second layer. The second layer delays the exposure of the first layer to the aqueous media. The second layer comprises at least one polymer, the first polymer.

[0019] In some embodiments, the first polymer comprises a soluble film-forming polymer. By "soluble" it is meant that the polymer is soluble in aqueous

media, which means that at least about 50% of the polymer has dissolved within one hour after exposure to the aqueous media. It is understood that some polymers disperse in aqueous solutions. This dispersion is not the same as dissolving. For a compound or polymer to be soluble, there needs to be a concentration of the compound or polymer in the solvent having solute-solvent interactions, as understood in the chemical arts.

[0020] In some embodiments, the first polymer is a sugar or a polysaccharide. In some of these embodiments, the sugar or polysaccharide is selected from the group consisting of cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, maltodextrin, sucrose, modified starch, a salt of alginic acid, soluble gums, and carageenan. In other embodiments, the first polymer is polyvinylpyrrolidone (PVP) or polyvinylpolypyrrolidone (PVPP).

[0021] In some embodiments, the soluble-forming polymer is a mixture of two or more polymers. In some embodiments, the mixture comprises hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC).

[0022] In some embodiments, hydroxypropylmethylcellulose is present in between about 1% to about 50% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 2% to about 40% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 5% to about 30% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 7% to about 25% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 8% to about 15% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 8% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 10% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 12% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 15% of the total weight of the bead.

[0023] In some embodiments, hydroxypropylcellulose is present in between about 1% to about 90% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in between about 5% to about 40% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is

present in between about 10% to about 30% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in between about 15% to about 25% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in between about 20% to about 25% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in about 21.50% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in about 22.25% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in about 22.75% of the total weight of the bead. In some embodiments, hydroxypropylcellulose is present in about 24.50% of the total weight of the bead.

[0024] In some embodiments, the second layer further comprises an insoluble film-forming polymer. By "insoluble" it is meant that the polymer is insoluble in aqueous media, which means that at most about 10% of the polymer has dissolved within one hour after exposure to the aqueous media. The presence of the insoluble film-forming polymer in the second layer causes greater delay in the exposure of the first layer to the aqueous media. The insoluble film-forming polymer and the soluble film-forming polymer form a matrix where upon exposure to the aqueous media the soluble polymer dissolves leaving pores in a network of insoluble polymer through which pores the API in the first layer leaches out into the aqueous media.

[0025] In some embodiments, the insoluble film-forming polymer is a polysaccharide. In some of these embodiments, the polysaccharide is selected from the group consisting of ethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and insoluble gums. In other embodiments, the insoluble film-forming polymer is selected from the group consisting of a polymethacrylate, a polyvinyl alcohol, shellac, and polyvinyl acetate phthalate.

[0026] In some embodiments, ethylcellulose is present in between about 1% to about 90% of the total weight of the bead. In some embodiments, ethylcellulose is present in between about 5% to about 40% of the total weight of the bead. In some embodiments, ethylcellulose is present in between about 10% to about 30% of the total weight of the bead. In some embodiments, ethylcellulose is present in between about 15% to about 25% of the total weight of the bead. In some embodiments, ethylcellulose is present in between about 20% to about 25% of the total weight of the bead. In some embodiments, ethylcellulose is present in about

21.50% of the total weight of the bead. In some embodiments, ethylcellulose is present in about 22.25% of the total weight of the bead. In some embodiments, ethylcellulose is present in about 22.75% of the total weight of the bead. In some embodiments, ethylcellulose is present in about 24.50% of the total weight of the bead.

[0027] In some embodiments, the second layer comprises hydroxypropylcellulose and ethylcellulose. In some embodiments, the ratio of hydroxypropylcellulose to ethylcellulose is between about 5:1 to about 1:5 by weight. In some embodiments, the ratio of hydroxypropylcellulose to ethylcellulose is between about 4:1 to about 1:4 by weight. In some embodiments, the ratio of hydroxypropylcellulose to ethylcellulose is between about 3:1 to about 1:3 by weight. In some embodiments, the ratio of hydroxypropylcellulose to ethylcellulose is between about 2:1 to about 1:2 by weight. In some embodiments, the ratio of hydroxypropylcellulose to ethylcellulose is about 1:1 by weight.

[0028] In some embodiments, the first bead further comprises a de-tackifier or a glidant. In some embodiments, the de-tackifier or glidant is an inert mineral. An inert mineral is a mineral, i.e., an inorganic compound or salt, that is pharmaceutically acceptable and does not interfere with the pharmacological action of the therapeutic compound. In some embodiments, the inert mineral is a mineral of magnesium. In other embodiments, the mineral of magnesium is magnesium silicate. In certain embodiments, the de-tackifier or glidant is selected from the group consisting of talc, a monoglyceride, a diglyceride, glyceryl monostearate, calcium stearate, and magnesium stearate.

[0029] In some embodiments, the de-tackifier or glidant is present in between about 1% to about 50% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in between about 2% to about 40% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in between about 3% to about 20% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in between about 4% to about 10% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 4% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 4.5% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 5% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 5.5% of

the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 6% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 6.5% of the total weight of the bead.

[0030] In some embodiments, the first polymer is, or comprises, a lipid excipient. The lipid excipient can be selected from the group consisting of glyceryl behenate, glycerol esters of fatty acids, glyceryl dibehenate, behenoyl macrogoglycerides, glyceryl distearate, glycerol distearate, glyceryl palmitostearate, lauroyl macrogoglycerides, stearoyl macrogoglycerides, abitec products, glyceryl mono-oleate, medium chain mono- & diglycerides, glyceryl monocaprylate, glyceryl tricaprylate/caprate/stearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated soybean oil and castor wax, polyoxyethylene 8 caprylic/capric glycerides, polyoxyethylene 6 caprylic/capric glycerides, polyoxyethylene 32 lauric glycerides, polyoxyethylene 6 prop. Glycol esters, polyoxyethylene 7 coconut glycerides, polyoxyethylene 30 coconut glycerides, polyoxyethylene 80 coconut glycerides, polyoxypropylene 15 stearyl ether, polyoxyethylene 26 glyceryl ether, polyoxyethylene 35 soybean glycerides, polyoxyethylene 20 sorbitol, polyoxypropylene 3 myristyl ether, polyoxypropylene 10 cetostearyl ether, palm kernelamide diethanolamide, triglycerol mono-oleate, sasol products, hydrogenated coco-glycerides, cetyl palmitate, trimyristin, tripalmitin, tristearin, hydrogenated palm oil, glyceryl monostearate, glyceryl stearate, cetearyl alcohol, cetyl alchohol, capric triglyceride, acetylated glycerides, glyceryl cocoate, and polyethylene glycol.

[0031] In some embodiments, the first bead further comprises a plasticizer. In some embodiments, the plasticizer is selected from the group consisting of a phthalate-based plasticizer, a trimellitate, an adipate-based plasticizer, a sebacate-based plasticizer, an organophosphate, a maleate, a sulfonamide, a glycols or polyether, an acetylated monoglyceride, and an alkyl citrate.

[0032] In some embodiments, the phthalate-based plasticizer is selected from the group consisting of bis(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), bis(n-butyl)phthalate (DnBP, DBP), butyl benzyl phthalate (BBzP), diisodecyl phthalate (DIDP), di-n-octyl phthalate (DOP or DnOP), diisooctyl phthalate (DIOP), diethyl phthalate (DEP), diisobutyl phthalate (DIBP), and di-n-hexyl phthalate. In some embodiments, the trimellitate is selected from the group consisting of trimethyl trimellitate (TMTM), tri-(2-ethylhexyl) trimellitate (TEHTM-

MG), tri-(n-octyl,n-decyl) trimellitate (ATM), tri-(heptyl,nonyl) trimellitate (LTM), and n-octyl trimellitate (OTM). In some embodiments, the adipate-based plasticizer is selected from the group consisting of bis(2-ethylhexyl)adipate (DEHA), dimethyl adipate (DMAD), monomethyl adipate (MMAD), and dioctyl adipate (DOA). In some embodiments, the sebacate-based plasticiser is dibutyl sebacate (DBS). In some embodiments, the maleate is dibutyl maleate (DBM) or diisobutyl maleate (DIBM). In some embodiments, the sulfonamide is selected from the group consisting of ortho or para N-ethyl toluene sulfonamide (ETSA), N-(2-hydroxypropyl) benzene sulfonamide (HP BSA), and N-(n-butyl) benzene sulfonamide (BBSA-NBBS). In some embodiments, the organophosphate is tricresyl phosphate (TCP) or tributyl phosphate (TBP). In some embodiments, the glycol or polyether is selected from the group consisting of triethylene glycol dihexanoate (3G6, 3GH), tetraethylene glycol diheptanoate (4G7), and polyethylene glycol. In some embodiments, the alkyl citrate is selected from the group consisting of Triethyl citrate (TEC), acetyl triethyl citrate (ATEC), tributyl citrate (TBC), acetyl tributyl citrate (ATBC), trioctyl citrate (TOC), acetyl trioctyl citrate (ATOC), trihexyl citrate (THC), acetyl trihexyl citrate (ATHC), butyryl trihexyl citrate (BTHC, trihexyl o-butyryl citrate), and trimethyl citrate (TMC). In some embodiments, the plasticizer is selected from the group consisting of dibutyl sebacate, polyethylene glycol, glycerin, triacetin, diethyl phthalate, propylene glycol, triethyl citrate, mineral oil, an acetylated monoglyceride, and oleic acid.

[0033] In some embodiments, the plasticizer is present in between about 1% to about 50% of the total weight of the bead. In some embodiments, the plasticizer is present in between about 2% to about 40% of the total weight of the bead. In some embodiments, the plasticizer is present in between about 3% to about 20% of the total weight of the bead. In some embodiments, the plasticizer is present in between about 4% to about 10% of the total weight of the bead. In some embodiments, the plasticizer is present in about 4% of the total weight of the bead. In some embodiments, the plasticizer is present in about 4.5% of the total weight of the bead. In some embodiments, the plasticizer is present in about 5% of the total weight of the bead. In some embodiments, the plasticizer is present in about 5.5% of the total weight of the bead. In some embodiments, the plasticizer is present in about 6% of the total weight of the bead. In some embodiments, the plasticizer is present in about 6.5% of the total weight of the bead.

[0034] In some embodiments, the weight of the second layer is between about 50% to about 300% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is between about 75% to about 250% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 75% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 100% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 125% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 150% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 175% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 200% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 225% of the weight of the bead prior to the application of the second layer. In some embodiments, the weight of the second layer is about 250% of the weight of the bead prior to the application of the second layer.

MUSCARINIC ANTAGONIST BEADS

[0035] In another aspect, disclosed herein are pharmaceutical compositions comprising a plurality of second beads each comprising:

a core; and

a first layer comprising a muscarinic antagonist or a pharmaceutically acceptable salt thereof.

[0036] In some embodiments, the muscarinic antagonist is present as the free base. In other embodiments, the muscarinic antagonist is present as a pharmaceutically acceptable salt. Pharmaceutically acceptable salts are defined above. In some embodiments, the muscarinic antagonist is selected from the group consisting of tolterodine, 5-hydroxymethyl tolterodine, fesoterodine, oxybutynin, solifenacin, darifenacin, trospium, imidafenacin, propiverine, and dicyclomine. In some embodiments, the tolterodine is tolterodine tartrate. In other embodiments, the oxybutynin is oxybutynin chloride.

[0037] In some embodiments, the core of the plurality of the second beads is comprised of the same material as the core of the plurality of the first beads, discussed above.

[0038] In some embodiments, the core comprises between about 10% to about 90% of the total weight of the finally-formulated bead. In some embodiments, the core comprises between about 25% to about 85% of the total weight of the finally-formulated bead. In some embodiments, the core comprises between about 40% to about 80% of the total weight of the finally-formulated bead. In some embodiments, the core comprises about 80% of the total weight of the finally-formulated bead. In some embodiments, the core comprises about 75% of the total weight of the finally-formulated bead. In some embodiments, the core comprises about 85% of the total weight of the finally-formulated bead.

[0039] In some embodiments, a solution of the API (i.e., the muscarinic antagonist), or a pharmaceutically acceptable salt thereof, is prepared and then sprayed onto the core and then dried. The act of spraying and drying causes a layer (the first layer) of the API to form over the bead. In some embodiments, the solution comprises a polymer that causes the API to more efficiently adhere to the core. The amount of the API present in the dosage form can be controlled by controlling the thickness of the first layer. The thicker the first layer the more API is present in the dosage form. Once the first layer is exposed to aqueous media, for example gastric or intestinal juice, the tolterodine contained therein immediately dissolves into the aqueous medium. Methods of applying the first layer uniformly onto the core are well-known in the art.

[0040] In some embodiments, the first layer comprises between about 1% to about 50% of the total weight of the bead. In some embodiments, the first layer comprises between about 2% to about 40% of the total weight of the bead. In some embodiments, the first layer comprises between about 4% to about 25% of the total weight of the bead. In some embodiments, the first layer comprises between about 5% to about 15% of the total weight of the bead. In some embodiments, the first layer comprises between about 5.5% to about 10% of the total weight of the bead. In some embodiments, the first layer comprises about 6% of the total weight of the bead. In some embodiments, the first layer comprises about 6.5% of the total weight of the bead. In some embodiments, the first layer comprises about 7% of the total weight of

the bead. In some embodiments, the first layer comprises about 8% of the total weight of the bead.

[0041] In some embodiments, the first layer comprises a soluble film-forming polymer, as defined above.

[0042] In some embodiments, hydroxypropylmethylcellulose is present in between about 1% to about 50% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 2% to about 40% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 5% to about 30% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 7% to about 25% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in between about 8% to about 15% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 8% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 10% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 12% of the total weight of the bead. In some embodiments, hydroxypropylmethylcellulose is present in about 15% of the total weight of the bead.

[0043] In some embodiments, the second bead further comprises a de-tackifier or a glidant, as defined above. In some embodiments, the de-tackifier or glidant is present in between about 1% to about 50% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in between about 2% to about 40% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in between about 3% to about 20% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in between about 4% to about 10% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 3% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 3.5% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 4% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 4.5% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 5% of the total weight of the bead. In some embodiments, the de-tackifier or glidant is present in about 5.5% of the total weight of the bead.

[0044] In some embodiments, the first layer further comprises a lipid excipient. The lipid excipient can be selected from the group consisting of glyceryl behenate, glycerol esters of fatty acids, glyceryl dibehenate, behenoyl macrogoglycerides, glyceryl distearate, glycerol distearate, glyceryl palmitostearate, lauroyl macrogoglycerides, stearoyl macrogoglycerides, abitec products, glyceryl mono-oleate, medium chain mono- & diglycerides, glyceryl monocaprylate, glyceryl tricaprylate/caprate/stearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated soybean oil and castor wax, polyoxyethylene 8 caprylic/capric glycerides, polyoxyethylene 6 caprylic/capric glycerides, polyoxyethylene 32 lauric glycerides, polyoxyethylene 6 prop. glycol esters, polyoxyethylene 7 coconut glycerides, polyoxyethylene 30 coconut glycerides, polyoxyethylene 80 coconut glycerides, polyoxypropylene 15 stearyl ether, polyoxyethylene 26 glyceryl ether, polyoxyethylene 35 soybean glycerides, polyoxyethylene 20 sorbitol, polyoxypropylene 3 myristyl ether, polyoxypropylene 10 cetostearyl ether, palm kernelamide diethanolamide, triglycerol mono-oleate, sasol products, hydrogenated coco-glycerides, cetyl palmitate, trimyristin, tripalmitin, tristearin, hydrogenated palm oil, glyceryl monostearate, glyceryl stearate, cetearyl alcohol, cetyl alchohol, capric triglyceride, acetylated glycerides, glyceryl cocoate, and polyethylene glycol.

[0045] In some embodiments, the second bead further comprises a plasticizer, as defined above. In some embodiments, the plasticizer is polyethylene glycol. In certain embodiments, the polyethylene glycol is PEG 400.

[0046] In some embodiments, the plasticizer is present in between about 0.1% to about 50% of the total weight of the bead. In some embodiments, the plasticizer is present in between about 0.1% to about 40% of the total weight of the bead. In some embodiments, the plasticizer is present in between about 0.1% to about 5% of the total weight of the bead. In some embodiments, the plasticizer is present in between about 0.2% to about 2% of the total weight of the bead. In some embodiments, the plasticizer is present in about 0.1% of the total weight of the bead. In some embodiments, the plasticizer is present in about 0.15% of the total weight of the bead. In some embodiments, the plasticizer is present in about 0.2% of the total weight of the bead. In some embodiments, the plasticizer is present in about 0.25% of the total weight of the bead. In some embodiments, the plasticizer is present in about 0.3% of the total weight of the bead. In some embodiments, the plasticizer is present

in about 0.35% of the total weight of the bead. In some embodiments, the plasticizer is present in about 0.4% of the total weight of the bead.

[0047] In some embodiments, the second beads further comprise a second layer. In some embodiments, the second layer comprises ingredients similar to the first layer, discussed above, except that the second layer does not have any API. In some embodiments, the first layer and the second layer have identical set of ingredients, whereas in other embodiments, the first and second layers have different combination of ingredients.

PHARMACEUTICAL FORMULATIONS

[0048] In another aspect, disclosed herein are pharmaceutical formulations comprising one of the following combinations of the above beads: a) a plurality of the first beads; b) a plurality of the second beads; or c) a plurality of the first beads and a plurality of the second beads.

[0049] The disclosed pharmaceutical formulations contain sufficient number of beads to provide a single administrable dose to a subject. In some embodiments, a single administrative dose for the muscarinic agonist is between 0.5-50 mg. In certain embodiments, a single administrable dose of pilocarpine is selected from the group consisting of 3 mg, 4 mg, 5 mg, 6 mg, 10 mg, 11 mg, and 12 mg. In other embodiments, a single administrable dose of cevimeline is selected from the group consisting of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 50 mg, and 60 mg. In certain embodiments, a single administrable dose for the muscarinic antagonist is between 0.1-100 mg. In certain embodiments, a single administrative dose is selected from the group consisting of 0.1 mg, 0.2 mg, 0.4 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 7.5 mg, 8 mg, 10 mg, 12 mg, 15 mg, 30 mg, and 60 mg.

[0050] In some embodiments, the pharmaceutical formulations are in the form of capsules. The capsules may include push-fit capsules made of gelatin, push-fit capsules, for example those made of hydroxypropylmethylcellulose, banded push-fit capsules, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol.

[0051] In some embodiments, the pharmaceutical formulations are in the form of dose sipping straws. In some embodiments, the beads are filled into a straw and a patient then drinks liquid through the straw, and through the process of

drinking, the liquid pulled through the straw brings the beads into the mouth along with the liquid.

[0052] In some embodiments, the pharmaceutical formulations are in the form of dry sachets. In some embodiments, the beads are sprinkled onto food or mixed into a drink from dry sachet, and taken orally. For the dosage to be effective, the disclosed beads are filled into a sachet pouch, along with additional excipients needed to form a readily dispersible suspension. When the pouch is opened and the contents are poured over food or into a drink, the beads and additional excipients are mixed with the food or the drink, and form a palatable dispersion that is ingested by the subject. Excipients, such as salivants and glidants, are added for the contents to be easily swallowed with a minimum of chewing so that the coatings are not broken in the mouth.

[0053] In some embodiments, the pharmaceutical formulations are in the form of ready-to-use sachets. In some embodiments, the beads are premixed with an edible, high viscosity food substance (for example, yogurt, or energy gel), and the entire contents of the package is taken orally. Excipients, such as salivants and glidants, are added for the contents to be easily swallowed with a minimum of chewing so that the coatings are not broken in the mouth.

[0054] In some embodiments, the pharmaceutical formulations are in the form of suspensions. In some embodiments, the suspensions comprise ingredients such as glycerin, microcrystalline cellulose, carboxymethyl cellulose sodium, sorbitol solution, xanthan gum, and the like, and various colorings and flavorings to make the suspension palatable for pediatric or geriatric use.

[0055] In some embodiments, the first beads disclosed above, having pilocarpine or a pharmaceutically acceptable salt thereof, and the first and second layers, are coated with a third layer comprising tolterodine, or a pharmaceutically acceptable salt thereof. The third layer is the same as, or similar to, the first layer of the second beads discussed above. In certain embodiments, the tolterodine-coated first bead is further coated with a fourth layer, which is the same as, or similar to, the second layer of the second beads discussed above.

EXAMPLES

Example 1: Materials Used in the Bead Manufacturing Process

[0056] The raw materials listed in Table 1 were used in the production of the pilocarpine and tolterodine beads.

Table 1. Components Used for Bead Production

Generic Name	Trade Name	Supplier
Pilocarpine Hydrochloride	Pilocarpine HCl	Boehringer Ingelheim
Tolterodine Tartrate	Tolterodine tartrate	Medichem
Ethylcellulose	Ethylcellulose N10	Hercules
Ethylcellulose	Ethylcellulose N7	Hercules
Hydroxypropyl Methylcellulose	Pharmacoat 606	Shin Etsu
Hydroxypropyl Cellulose	Klucel EF	Hercules
Polyethylene Glycol 400	Carbowax 400	Dow
Dibutyl Sebacate	Dibutyl Sebacate	Vertellus
Talc	Luzenac Talc	Minerals and Pigments
Dehydrated Alcohol, 200 proof	Ethanol	Spectrum
Microcrystalline Cellulose Beads	Cellets 700	Glatt
GMS Emulsion	Plasacryl	Emerson
Microcrystalline Cellulose	Avicel PH 101	FMC
Milled Lactose	Pharmatose 200M	DMV
Croscarmellose Sodium	Ac-Di-Sol	FMC
Crospovidone	Polyplasdone XL-10	ISP
Gelatin Capsules	Conisnaps, size 2	Capsugel
Sterile water for Irrigation	Water	Hospira
Deionized water	Deionized water	N/A

[0057] The equipment listed in Table 2 was used for the preparation of the beads.

Table 2. Equipment Used for Bead Production

Equipment	Manufacturer	Location
FLM-1 fluid bed	Vector Corporation	Marion, IA
FLM-3 fluid bed	Vector Corporation	Marion, IA
DG-L1 Extruder	LCI	Charlotte, NC
QJ-230 Spheronizer	LCI	Charlotte, NC
Blend Master V-blender	Patterson Kelly	East Stroudsburg, PA
In Cap Automatic Encapsulator	Dott. Bonapace & C.	Milan, Italy
ProFill 100 Manual Encapsulator	Capsugel	Greenwood, SC
Portable Dehumidifier	DRI-EAZ	Burlington, WA

Example 3: Dissolution Rate Determination

[0058] This method describes the procedure for the determination of the dissolution rate of the pilocarpine HCl and tolterodine tartrate combination formulations by using a reverse-phase, gradient, high-pressure liquid chromatography (HPLC) method, using techniques well-known in the art.

[0059] Stock solutions of pilocarpine HCl and tolterodine tartrate were prepared as working standards. Beads containing pilocarpine HCl and tolterodine tartrate are separately mixed with a fixed volume of 0.1 N HCl. At fixed time points after the mixing has begun, aliquots of the dissolution mixtures are injected into HPLC followed by several aliquots of the working standards. The amounts of released (dissolved) tolterodine and pilocarpine entities of formulations were calculated using the corresponding peak areas of tolterodine and pilocarpine.

[0060] A USP 2 Paddles method with the following conditions was employed to determine dissolution of various formulations.

Dissolution media:	0.1 N HCl
Agitation Rate:	50 RPM
Vessel Temp:	37 °C±0.5 °C
Sample Volume:	1.0mL
Disso Volume:	500mL

Example 3: Bead Formation

[0061] Beads were produced by drug layering microcrystalline cellulose beads with aqueous, cellulosic coating systems containing pilocarpine HCl or tolterodine tartrate. The beads were formulated into single dose units. The coating formulations are displayed in Tables 3 and 4 below:

Table 3. Sample A: Tolterodine Tartrate Drug Layering:

Component	**mg/unit**	**%w/w**
Microcrystalline Cellulose Beads	25.0	79.4
Tolterodine Tartrate	2.0	6.3
HPMC	3.1	9.8
Talc	1.1	3.5
PEG 400	0.3	1.0
Total	31.5	100.0

Table 4. Sample B: Pilocarpine HCl drug layering:

Component	mg/unit	%w/w
Microcrystalline Cellulose Beads	27.5	50.0
Pilocarpine HCl	11.0	20.0
HPMC	11.0	20.0
Talc	5.5	10.0
Total	55.0	100.0

[0062] Both coating solutions were applied to the Microcrystalline Cellulose (MCC) Pellets using a Vector FLM-1 fluid bed with a Wurster coating configuration. Beads were hand-filled into size 2 gelatin capsules and tested for dissolution using the procedure of Example 2. The dissolution data of the drug layered beads are shown in Tables 5 and 6:

Table 5. Sample A: Tolterodine Tartrate Release Data

% Dissolved at Time Point (min)							
Vessel #	**0**	**5**	**12**	**20**	**30**	**45**	**60**
V1	0	77	109	113	113	114	114
V2	0	71	100	104	106	108	108
V3	0	45	96	106	111	113	113
V4	0	43	100	109	112	113	113
V5	0	61	100	105	108	110	110
V6	0	43	92	107	111	113	113
Mean	0	56	99	107	110	111	112
SD	0	15.1	5.7	3.2	2.5	2.4	2.3
%RSD	0.00%	26.73%	5.74%	2.96%	2.29%	2.17%	2.04%

Table 6. Sample B: Pilocarpine HCl Release Data

% Dissolved at Time Point (min)						
Vessel #	**0**	**10**	**20**	**30**	**45**	**60**
V1	0	100	104	105	105	105
V2	0	99	106	106	106	106
V3	0	102	106	107	106	106
V4	0	101	106	106	107	107
V5	0	105	108	108	108	108
V6	0	93	109	109	109	109
Mean	0	100	107	107	107	107
SD	0	4.0	1.8	1.5	1.5	1.5
%RSD		4.0%	1.7%	1.4%	1.4%	1.4%

[0063] Both types of drug layered beads were top-coated. The tolterodine beads were coated with a thin, immediate release HPMC based coating system to

ensure no tolterodine tartrate was lost from erosion. The topcoat for the pilocarpine HCl beads was developed in rounds 2-5 of development.

Example 4: Bead Formation

[0064] The development in this example focused on the use of several types and grades of cellulosic polymers in order to form a semi-permeable barrier that would delay release. All coatings applied were at relatively low weight gains, no higher than 50%. It was determined that the application of high weight gains produced the desired delayed release profile. The formulations and release profiles are summarized in Table 7 below:

Table 7. Formulations

Reference	Film Component	% w/w
A	HPMC 606	40
	EC N10	40
	Talc	20
C	HPC EF	24
	EC N7	56
	Talc	20
D	HPC EF	32
	EC N7	48
	Talc	20
E	HPC EF	24
	EC N10	56
	Talc	20
F	HPC EF	87
	Plasacryl	13
G	EC N7	90.9
	Dibutyl Sebacate	9.1
H	EC N10	90.9
	Dibutyl Sebacate	9.1

[0065] The dissolution data of the beads of Samples F and G, obtained using the procedure of Example 2, are shown in Tables 8 and 9:

Table 8. Sample F Dissolution Data

% Dissolved at Time Point (min)										
Vessel #	**0**	**10**	**20**	**30**	**45**	**60**	**75**	**90**	**120**	**Infinity**
V1	0	9	48	71	84	89	96	99	101	101

V2	0	9	50	77	92	95	96	97	97	97
Mean	0	9	49	74	88	92	96	98	99	99
SD	0	0.0	1.4	4.2	5.7	4.2	0.0	1.4	2.8	2.8
%RSD		0.0%	2.9%	5.7%	6.4%	4.6%	0.0%	1.4%	2.9%	2.9%

Table 9. Sample G Dissolution Data

% Dissolved at Time Point (min)										
Vessel #	**0**	**10**	**20**	**30**	**45**	**60**	**75**	**90**	**120**	**Infinity**
V1 (1%)*	0	53	73	84	92	96	99	100	102	102
V2 (1%)*	0	55	73	84	93	99	102	103	104	104
Mean	0	54	73	84	93	98	101	102	103	103
SD	0	1.4	0.0	0.0	0.7	2.1	2.1	2.1	1.4	1.4
%RSD		2.6 %	0.0%	0.0%	0.8%	2.2%	2.1%	2.1%	1.4%	1.4%
V3 (4%)*	0	2	8	21	42	59	71	81	92	96
V4 (4%)*	0	2	9	22	43	59	71	82	91	95
Mean	0	2	9	22	43	59	71	82	92	96
SD	0	0.0	0.7	0.7	0.7	0.0	0.0	0.7	0.7	0.7
%RSD		0.0 %	8.3%	3.3%	1.7%	0.0%	0.0%	0.9%	0.8%	0.7%
V5 (8%)*	0	1	4	7	14	22	32	41	57	65
V6 (8%)*	0	1	3	5	11	19	28	36	52	61
Mean	0	1	4	6	13	21	30	39	55	63
SD	0	0.0	0.7	1.4	2.1	2.1	2.8	3.5	3.5	2.8
%RSD		0.0 %	20.2 %	23.6 %	17.0 %	10.3%	9.4%	9.2%	6.5%	4.5%

*: The percentages refer to different film thicknesses.

Example 5: Bead Formation

[0066] In this example, swellable beads containing pilocarpine HCl were produced. First, placebo beads were produced in order to compare two common super-disintegrants. The criterion for super-disintegrant selection was volume increase as the beads were placed in 0.1 N HCl. The formulations and results are below in Table 9:

Table 9. Placebo bead formulations

Experiment Reference	**Bead Component**	**% w/w**
I	Microcrystalline Cellulose	45
	Lactose	45
	Croscarmellose Sodium	10
J	Microcrystalline Cellulose	45
	Lactose	45

	Crospovidone	10

[0067] Two swellable pilocarpine HCl bead formulations were produced, with differing quantities of pilocarpine. These beads were then each coated with the same ethylcellulose based coating system and tested for dissolution. The formulations and results are set forth below in Table 10.

Table 10. Pilocarpine HCl swellable bead formulations

Experiment Reference	**Component**	**% w/w**
K bead	Microcrystalline Cellulose	40.6
	Lactose	40.6
	Croscarmellose Sodium	8.8
	Pilocarpine HCl	10.0
L bead	Microcrystalline Cellulose	43.1
	Lactose	43.1
	Crospovidone	8.8
	Pilocarpine HCl	5.0
K and L coating formulation	Ethylcellulose N7	90.9
	Dibutyl Sebacate	9.1

[0068] As shown in the dissolution data in Table 11, the formulations had the desired delayed release, obtained using the procedure of Example 2.

Table 11. Samples K and L Dissolution Data

% Dissolved at Time Point (min)							
Vessel #	**0**	**10**	**20**	**30**	**45**	**60**	**Infinity**
K-1 (4%)	0	1	4	17	44	61	72
K-2 (8%)	0	0	0	1	3	7	12
K-3 (12%)	0	0	0	0	1	2	3
L-1 (4%)	0	1	4	12	29	42	53
L-2 (8%)	0	0	0	1	2	5	10
L-3 (12%)	0	0	0	1	1	3	4

Example 5: Bead Formation

[0069] This example focused on coating drug-layered microcrystalline cellulose cores with cellulosic polymers to high weight gains (up to 200%). The first coating formulation consisted of a soluble polymer, hydroxypropylcellulose (HPC), which forms a hydrogel that delays release. The second formulation consisted of a 1:1

ratio of HPC and ethylcellulose. The thickness of both types of films directly correlated to the delay in release of pilocarpine HCl. The formulations for each prototype are shown below in Table 12.

Table 12. High weight gain cellulosic coatings

Experiment Reference	Film Component	% w/w
M, N	HPC EF	45.45
	EC N10	45.45
	Talc	9.10
O	HPC EF	87
	Plasacryl	13

[0070] Beads having the following weight gains were produced: 75%, 100%, 125%, 150%, 175%, and 200%. This set of beads exhibited a wide range of lag times, followed by immediate release. The delay in release is controlled by the thickness of the film. The dissolution data, obtained using the procedure of Example 2, are shown in Tables 13 and 14.

Table 13. Samples M and N Dissolution Data

% Dissolved at Time Point (min)									
Sample Description	**0**	**5**	**12**	**20**	**30**	**45**	**60**	**75**	**Infinity**
M-1 (75%)	0	0	0	12	76	94	96	98	98
M-2 (100%)	0	0	0	1	33	90	95	96	96
N-1 (125%)	0	0	0	0	2	74	98	100	100
N-2 (150%)	0	0	1	0	0	27	89	98	99
N-3 (175%)	0	0	0	0	0	6	68	96	99
N-4 (200%)	0	0	0	1	0	1	28	83	93

Table 14. Sample O Dissolution Data

% Dissolved at Time Point (min)									
Sample Description	**0**	**5**	**12**	**20**	**30**	**45**	**60**	**75**	**Infinity**
O-1 (80%)	0	0	5	25	48	67	76	80	82
O-2 (100%)	0	0	2	15	40	62	72	78	83
O-3 (120%)	0	0	0	3	23	53	70	79	86
O-4 (140%)	0	0	1	3	15	46	65	76	83
O-5 (150%)	0	0	0	2	14	48	66	76	83

Example 6: Cevimeline Bead Formation

[0071] Cevimeline beads are produced in substantially the same manner as pilocarpine beads, as described above, except that cevimeline is used instead of pilocarpine.

Example 7: Muscarinic Antagonist Bead Formation

[0072] Beads containing a muscarinic antagonist selected from the group consisting of the muscarinic antagonist is selected from the group consisting of 5-hydroxymethyl tolterodine, fesoterodine, oxybutynin, solifenacin, darifenacin, trospium, imidafenacin, propiverine, and dicyclomine are prepared in substantially the same manner as tolterodine beads, as described above, except that the specific muscarinic antagonist is used instead of tolterodine.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a plurality of first beads each comprising:

a core;

a first layer comprising pilocarpine, or cevimeline, or a pharmaceutically acceptable salt thereof; and

a second layer comprising a first polymer.

2. The pharmaceutical composition of claim 1, wherein the core comprises a cellulose polymer, or silicon dioxide, or a sugar, selected from the group consisting of glucose, sucrose, lactose, mannitol, xylitol, and sorbitol.

3. The pharmaceutical composition of claim 1, wherein the core comprises between about 10% to about 50% of the total weight of the finally-formulated bead.

4. The pharmaceutical composition of claim 1, wherein the first layer comprises between about 1% to about 50% of the total weight of the bead.

5. The pharmaceutical composition of claim 1, wherein the first polymer comprises a soluble film-forming polymer selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, maltodextrin, sucrose, modified starch, a salt of alginic acid, carageenan, polyvinylpyrrolidone (PVP) or polyvinylpolypyrrolidone (PVPP).

6. The pharmaceutical composition of claim 1, wherein the second layer further comprises an insoluble film-forming polymer selected from the group consisting of ethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, insoluble gums, a polymethacrylate, a polyvinyl alcohol, shellac, and polyvinyl acetate phthalate.

7. The pharmaceutical composition of claim 1, wherein the bead further comprises a de-tackifier or a glidant selected from the group consisting of talc, glyceryl monostearate, calcium stearate, and magnesium stearate.

8. The pharmaceutical composition of claim 1, wherein the bead further comprises a plasticizer selected from the group consisting of a phthalate-based plasticizer, a trimellitate, an adipate-based plasticizer, a sebacate-based plasticizer, an organophosphate, a maleate, a sulfonamide, a glycols or polyether, an acetylated monoglyceride, and an alkyl citrate.

9. The pharmaceutical composition of claim 1, wherein the first layer further comprises a lipid excipient selected from the group consisting of glyceryl behenate, glycerol esters of fatty acids, glyceryl dibehenate, behenoyl macrogoglycerides, glyceryl distearate, glycerol distearate, glyceryl palmitostearate, lauroyl macrogoglycerides, stearoyl macrogoglycerides, abitec products, glyceryl mono-oleate, medium chain mono- & diglycerides, glyceryl monocaprylate, glyceryl tricaprylate/caprate/stearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated soybean oil and castor wax, polyoxyethylene 8 caprylic/capric glycerides, polyoxyethylene 6 caprylic/capric glycerides, polyoxyethylene 32 lauric glycerides, polyoxyethylene 6 prop. glycol esters, polyoxyethylene 7 coconut glycerides, polyoxyethylene 30 coconut glycerides, polyoxyethylene 80 coconut glycerides, polyoxypropylene 15 stearyl ether, polyoxyethylene 26 glyceryl ether, polyoxyethylene 35 soybean glycerides, polyoxyethylene 20 sorbitol, polyoxypropylene 3 myristyl ether, polyoxypropylene 10 cetostearyl ether, palm kernelamide diethanolamide, triglycerol mono-oleate, sasol products, hydrogenated coco-glycerides, cetyl palmitate, trimyristin, tripalmitin, tristearin, hydrogenated palm oil, glyceryl monostearate, glyceryl stearate, cetearyl alcohol, cetyl alchohol, capric triglyceride, acetylated glycerides, glyceryl cocoate, and polyethylene glycol.

10. A pharmaceutical composition comprising a plurality of second beads each comprising:

a core; and

a first layer comprising a muscarinic antagonist or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of claim 10, wherein the muscarinic antagonist is selected from the group consisting of tolterodine, 5-hydroxymethyl tolterodine, fesoterodine, oxybutynin, solifenacin, darifenacin, trospium, imidafenacin, propiverine, and dicyclomine.

12. The pharmaceutical composition of claim 10, wherein the core comprises a cellulose polymer, or silicon dioxide, or a sugar, selected from the group consisting of glucose, sucrose, lactose, mannitol, xylitol, and sorbitol.

13. The pharmaceutical composition of claim 10, wherein the core comprises between about 10% to about 90% of the total weight of the finally-formulated bead.

14. The pharmaceutical composition of claim 10, wherein the first layer comprises between about 1% to about 50% of the total weight of the bead.

15. The pharmaceutical composition of claim 10, wherein the first polymer comprises a soluble film-forming polymer selected from the group consisting of hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, maltodextrin, sucrose, modified starch, a salt of alginic acid, carageenan, polyvinylpyrrolidone (PVP) or polyvinylpolypyrrolidone (PVPP).

16. The pharmaceutical composition of claim 10, wherein the bead further comprises:

a de-tackifier or a glidant selected from the group consisting of talc, glyceryl monostearate, calcium stearate, and magnesium stearate; and

a plasticizer selected from the group consisting of a phthalate-based plasticizer, a trimellitate, an adipate-based plasticizer, a sebacate-based plasticizer, an organophosphate, a maleate, a sulfonamide, a glycols or polyether, an acetylated monoglyceride, and an alkyl citrate.

17. The pharmaceutical composition of claim 10, further comprising a second layer, which comprises a soluble-film forming polymer.

18. The pharmaceutical composition of claim 10, wherein the first layer further comprises a lipid excipient selected from the group consisting of glyceryl behenate, glycerol esters of fatty acids, glyceryl dibehenate, behenoyl macrogoglycerides, glyceryl distearate, glycerol distearate, glyceryl palmitostearate, lauroyl macrogoglycerides, stearoyl macrogoglycerides, abitec products, glyceryl mono-oleate, medium chain mono- & diglycerides, glyceryl monocaprylate, glyceryl tricaprylate/caprate/stearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated soybean oil and castor wax, polyoxyethylene 8 caprylic/capric glycerides, polyoxyethylene 6 caprylic/capric glycerides, polyoxyethylene 32 lauric glycerides, polyoxyethylene 6 prop. glycol esters, polyoxyethylene 7 coconut glycerides, polyoxyethylene 30 coconut glycerides, polyoxyethylene 80 coconut glycerides, polyoxypropylene 15 stearyl ether, polyoxyethylene 26 glyceryl ether, polyoxyethylene 35 soybean glycerides, polyoxyethylene 20 sorbitol, polyoxypropylene 3 myristyl ether, polyoxypropylene 10 cetostearyl ether, palm kernelamide diethanolamide, triglycerol mono-oleate, sasol products, hydrogenated coco-glycerides, cetyl palmitate, trimyristin, tripalmitin, tristearin, hydrogenated palm oil, glyceryl monostearate, glyceryl stearate, cetearyl

alcohol, cetyl alchohol, capric triglyceride, acetylated glycerides, glyceryl cocoate, and polyethylene glycol.

19. A pharmaceutical formulation comprising:

a) a plurality of the first beads of claim 1;

b) a plurality of the second beads of claim 10; or

c) a plurality of the first beads of claim 1 and a plurality of the second beads of claim 10.

20. The pharmaceutical formulation of claim 19, comprising:

a) pilocarpine or cevimeline, or a pharmaceutically acceptable salt thereof, in a dose between 0.5-50 mg; and

b) a muscarinic antagonist, or a pharmaceutically acceptable salt thereof, in a dose between 0.1-100 mg.