another embodiment, the present method is directed to a method of preparing a pharmaceutical composition comprising coating about 20-25 mesh inert particles with an about 25 wt.% solids content drug layering composition comprising cyclobenzaprine or pharmaceutically acceptable salts, solvates, and/or esters thereof, and an aqueous organic solvent; drying the coated inert particles, thereby forming drug layered beads; coating the drug layered beads with an about 8-10 wt.% solids content seal coating composition comprising a pharmaceutically acceptable water soluble polymer and water; drying the coated drug layered beads, thereby forming IR beads (e.g., drug load: 25% w/w); coating the IR beads with an about 6 wt.% solids content ER coating composition comprising a pharmaceutically acceptable water-insoluble polymer and an optional plasticizer; drying the coated IR beads under an atmosphere having a dew point ranging from about 5-20°C, thereby forming ER beads; and optionally curing the sieved ER beads at about 60°C for up to about 4 hours, under an atmosphere having a dew point ranging from about 5-20°C.

another embodiment, the present method is directed to a method of preparing a pharmaceutical composition comprising coating about 20-25 mesh inert particles with an about 25 wt.% solids content drug layering composition comprising cyclobenzaprine or pharmaceutically acceptable salts, solvates, and/or esters thereof, and an aqueous organic solvent; drying the coated inert particles, thereby forming drug layered beads; coating the drug layered beads with an about 8-10 wt.% solids content seal coating composition comprising a pharmaceutically acceptable water soluble polymer and water; drying the coated drug layered beads, thereby forming IR beads (e.g., drug load: 25% w/w); coating the IR beads with an about 6 wt.% solids content ER coating composition comprising a pharmaceutically acceptable water-insoluble polymer and an optional plasticizer; drying the coated IR beads under an atmosphere having a dew point ranging from about 5-20°C, thereby forming ER beads; and optionally curing the sieved ER beads at about 60°C for up to about 4 hours, under an atmosphere having a dew point ranging from about 5-20°C.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The invention will be described in further detail with reference to the accompanying Figures wherein:

[0021] FIG. 1 shows the proposed target release profile for cyclobenzaprine hydrochloride MR (modified release) capsules.

[0022] FIG. 2 shows the simulated Day 1 plasma level following dosing of 1x10 mg Flexeril® given 3 times a day and 1x30 mg cyclobenzaprine HCl MR capsule given once-daily.

[0023] FIG. 3 shows a flow diagram of a cyclobenzaprine HCl MR capsule production process.

[0024] FIG. 4 shows the plasma concentration – time profiles of Cyclobenzaprine HCl modified-release (MR) capsules, 30 mg vs. Fexeril (Cyclobenzaprine HCl immediate-release (IR) tablets, 10 mg) x t.i.d. tested in pivotal PK clinical study.

[0025] FIG. 5 shows the actual and simulated *in-vitro* release profiles for CMR 30 mg (simulated profile was obtained using the PK parameters derived from the clinical study.

The present invention also provides any one of the embodiments disclosed below and indicated with the numbers 1 to 29.

1. A method of preparing a pharmaceutical composition comprising:

a) coating inert particles with a drug layering composition comprising cyclobenzaprine or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and a pharmaceutically acceptable solvent, thereby forming IR beads; and

b) coating the IR beads with an ER coating composition comprising a pharmaceutically acceptable water-insoluble polymer, under an atmosphere having a dew point ranging from about 5-20°C, thereby forming ER beads.

2. The method of claim 1, further comprising:

c) curing the ER beads at about 60°C for about 4-12 hours under an atmosphere having a dew point ranging from about 5-20°C.

3. The method of claim 1, further comprising coating the IR beads of step a) with a seal-coating composition comprising a pharmaceutically acceptable water-soluble polymer before said ER coating step b).

4. The method of claim 3, wherein said inert particles have a particle size of about 20-25 mesh.

5. The method of claim 1, wherein said seal-coating composition further comprises water.

6. The method of claim 1, wherein said coating steps a) and b) are carried out under an atmosphere having a dew point ranging from about 5-20°C.

7. The method of claim 1, wherein the ER coating composition further comprises a plasticizer.

8. The method of claim 7, wherein the ER coating composition is prepared by stirring the pharmaceutically acceptable water-insoluble polymer, plasticizer, and pharmaceutically acceptable solvent for at least about 1 hour after addition of the

plasticizer to the pharmaceutically acceptable water-insoluble polymer and pharmaceutically acceptable solvent.

9. The method of claim 8, wherein the pharmaceutically acceptable water-insoluble polymer, plasticizer, and pharmaceutically acceptable solvent are stirred for at least about 3 hours after addition of the plasticizer to the pharmaceutically acceptable water-insoluble polymer and pharmaceutically acceptable solvent.

10. The method of claim 1, wherein the drug layering composition further comprises cyclobenzaprine hydrochloride and about 50:50 acetone:water.

11. The method of claim 1, wherein the pharmaceutically acceptable water-soluble polymer comprises hydroxypropyl methylcellulose.

12. The method of claim 1, wherein the pharmaceutically acceptable water-insoluble polymer is selected from the group consisting of ethylcellulose, ethers of cellulose, esters of cellulose, cellulose acetate, cellulose butyrate, cellulose propionate, polyvinyl acetate, neutral copolymers based on ethyl acrylate and methyl methacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, pH-insensitive ammonio methacrylic acid copolymers, waxes, acetylated polysaccharides, polyurethanes, high molecular weight hydroxypropyl methylcellulose, polyacrylate and polymethacrylate polymers, and mixtures thereof.

13. The method of claim 1, wherein the pharmaceutically acceptable water-insoluble polymer comprises ethylcellulose.

14. The method of claim 7, wherein the plasticizer is selected from the group consisting of diethyl phthalate, triacetin, tributyl citrate, tri-ethyl citrate, acetyl tri-n-butyl citrate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and di-glycerides, glyceryl monostearate, glyceryl triacetate, glyceryl tributyrate, phthalates, citrates, glyceroltributyrate; sebacates, adipates, azelates, benzoates, chlorobutanol, polyethylene glycols, vegetable oils, olive oil, castor oil, mineral oil, fumarates, malates, oxalates, succinates, butyrates, cetyl alcohol esters, malonates,

polysorbates, glycerine, N-butylbenzenesulfonamide, N-methylpyrrolidone, and mixtures thereof.

15. The method of claim 7, wherein the plasticizer comprises diethyl phthalate.

16. The method of claim 7, wherein the ER coating composition comprises ethylcellulose and diethyl phthalate dissolved in a solvent comprising acetone and water at a acetone/water weight ratio ranging from about 85/15 to about 98/2.

17. The method of claim 7, wherein the ratio of water-insoluble polymer to plasticizer is about 9:1.

18. The method of claim 1, wherein the drug layering composition comprises cyclobenzaprine hydrochloride, and after drying, the drug layered beads comprise from about 20 wt.% to about 30 wt.% cyclobenzaprine hydrochloride.

19. The method of claim 18, wherein the drug layering composition comprises cyclobenzaprine hydrochloride, and after drying, the drug layered beads comprise about 25 wt.% cyclobenzaprine hydrochloride.

20. The method of claim 1, wherein the IR beads comprise about 2% of the pharmaceutically acceptable water soluble polymer.

21. The method of claim 1, wherein the ER beads comprise about 7% to about 12% of the pharmaceutically acceptable water insoluble polymer.

22. The method of claim 7, wherein the ER beads comprise about 9% of the pharmaceutically acceptable water-insoluble polymer and plasticizer.

23. The method of claim 1, wherein the ER beads provide a drug release profile that does not deviate by more than about 10% at any time point in the following dissolution pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released;

after 8 hours, from about 60-85% of the total active is released; and

optionally after 12 hours, from about 75-85% of the total active is released,

when tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1 N HCl at 37°C.

24. The method of claim 1, wherein the ER beads provide a drug release of about 20% to about 50% after 2 hours when tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1 N HCl at 37°C.

25. The method of claim 1, wherein said coating step b) is carried out under an atmosphere having a dew point ranging from about 6-17°C.

26. The method of claim 2, wherein said curing step c) is carried out under an atmosphere having a dew point ranging from about 6-17°C.

27. The method of claim 1, wherein said coating step a) is carried out under an atmosphere having a dew point ranging from about 6-17°C.

28. The method of claim 1, wherein the pharmaceutical composition comprises 30 mg of cyclobenzaprine HCl and provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 19.9 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} within the range of about 80% to 125% of about 736.6 ng·hr/mL following a single oral administration thereof.

29. The method of claim 1, wherein the pharmaceutical composition comprises 15 mg of cyclobenzaprine HCl and provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 8.3 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} within the range of about 80% to 125% of about 318.3 ng·hr/mL following a single oral administration thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The invention will be described in further detail with reference to the accompanying Figures wherein:

[0021] FIG. 1 shows the proposed target release profile for cyclobenzaprine hydrochloride MR (modified release) capsules.

[0022] FIG. 2 shows the simulated Day 1 plasma level following dosing of 1x10 mg Flexeril® given 3 times a day and 1x30 mg cyclobenzaprine HCl MR capsule given once-daily.

[0023] FIG. 3 shows a flow diagram of a cyclobenzaprine HCl MR capsule production process.

[0024] FIG. 4 shows the plasma concentration – time profiles of Cyclobenzaprine HCl modified-release (MR) capsules, 30 mg vs. Fexeril (Cyclobenzaprine HCl immediate-release (IR) tablets, 10 mg) x t.i.d. tested in pivotal PK clinical study.

[0025] FIG. 5 shows the actual and simulated *in-vitro* release profiles for CMR 30 mg (simulated profile was obtained using the PK parameters derived from the clinical study.