The present invention provides a layered pellet composition which comprises an inert core, a layer comprising a compound of formula I or a salt thereof as defined herein, and a controlled release layer comprising a rate controlling polymer.

The present invention also provides methods for the formation of such compositions. The compositions are useful for the treatment of CNS related disorders, including treatment resistant depression (TRD) and Fragile-X syndrome.

To reproducibly control drug release *in vivo*, a soluble polymer, such as polyvinyl alcohol, polyvinyl pyrrolidone, or hypermellose and pH independent insoluble polymer, such as ethylcellulose, polyvinylacetate, or polymethacrylate can be applied in a coating or a matrix. pH is the driving force for dissolution of poorly water-soluble, basic compounds through a membrane or gel layer. The dissolution rate and absorption rate of such compounds are affected by variation in physiological pH of GI tract. Thus, pH will still have a big impact on the solubility of such drugs.

Summary

In one aspect, there is provided a pharmaceutical composition in the form of a layered pellet comprising (a) an inert core; (b) a layer comprising a compound of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine; (c) a controlled release layer comprising a rate controlling polymer; and (d) a layer containing a pH responding polymer.

Brief Description of the Drawings

Figure 1 is the dissolution profile of the composition of Example 1 in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). This is a comparative example, not of the invention.

Figure 2 is the *in vitro* dissolution profile of the matrix tablet composition of Example 2 in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Figure 3 is the *in vitro* dissolution profile of the matrix pellet composition of Example 3 in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Figure 4 is the *in vitro* dissolution profile of the matrix pellet composition of Example 4 in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Figure 5 is the *in vitro* dissolution profile of the layered pellet composition of Example 5 in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Figure 6 is the *in vitro* dissolution profile of the layered pellet composition of Example 6 in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF).

Claims

1. A pharmaceutical composition in the form of a layered pellet comprising

a) an inert core;

b) a layer comprising a compound of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

c) a controlled release layer comprising a rate controlling polymer; and

d) a layer containing a pH responding polymer.

2. The composition according to claim 1, comprising

a) an inert core;

b) a layer containing a compound of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

c) optionally, a separation layer;

d) a controlled release layer containing a rate controlling polymer;

e) a layer containing a pH responding polymer; and

f) optionally, a layer containing a non-thermoplastic polymer.

3. The composition according to claim 1 or 2, wherein the inert core is selected from the group consisting of a sugar sphere, microcrystalline cellulose beads, and starch beads.

4. The composition according to any one of claims 1 to 3, wherein the inert core comprises a particle size below 3000 microns.

5. The composition according to any one of claims 1 to 4, wherein the inert core comprises a particles size below 2000 microns.

6. The composition according to any one of claims 1 to 5, wherein the inert core comprises an average particle size of 400 microns to 1500 microns.

7. The composition according to any one of claims 1 to 6, wherein the layer comprising the compound of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine further comprises a binder.

8. The composition according to any one of claims 1 to 7, wherein the binder is selected from the group consisting of hydrophilic polymers, water soluble polymers, and water insoluble polymers.

9. The composition according to any one of claims 1 to 8, wherein the hydrophilic polymer is selected from the group consisting of polyvinylpyrrolidone, a polyalkylene glycol, gelatin, polyvinyl alcohol, starch, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, and poly(meth)acrylates.

10. The composition according to any one of claims 1 to 9, wherein the rate controlling polymer is selected from the group consisting of ethyl cellulose, polyvinylacetate, polyvinylacetate:povidone copolymer, cellulose acetate, poly(meth)acrylates, and polyvinyl alcohol or mixtures thereof.

11. The composition according to any one of claims 1 to 10, wherein the layer comprising the rate controlling polymer further comprises a plasticizer.

12. The composition according to any one of claims 1 to 11, wherein the plasticizer is selected from the group consisting of dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, fractionated coconut oil, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, and medium-chain triglycerides.

13. The composition according to any one of claims 1 to 12, wherein the layer comprising the rate controlling polymer further comprises a water soluble or swellable material that alters the release rate of the controlled release layer.

14. The composition according to any one of claims 1 to 13, wherein the water soluble or swellabale poreforming material is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, cellulose acetate phthalate, ammonio methacrylate copolymer, poly(meth)acrylates, and mixtures thereof.

15. The composition according to any one of claims 1 to 14, wherein the composition comprises a separation layer.

16. The composition according to any one of claims 1 to 15, wherein the separation layer comprises a water soluble or permeable material.

17. The composition according to any one of claims 1 to 16, wherein the water soluble or permeable material is selected from the group consisting of polyvinylpyrrolidone, copovidone, polyalkylene glycol, gelatin, polyvinyl alcohol, starch, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, and poly(meth)acrylates and mixtures thereof.

18. The composition according to any one of claims 1 to 17, wherein the water soluble or permeable material is hydroxypropylmethyl cellulose.

19. The composition according to any one of claims 1 to 18, wherein the pH responding polymer is selected from the group consisting of hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, poly(meth)acrylates, and mixtures thereof.

20. The composition according to any one of claims 1 to 19, wherein the layer containing a pH responding polymer further comprises a plasticizer.

21. The composition according to any one of claims 1 to 20, wherein the plasticizer is selected from the group consisting of dibutylsebacate, propylene glycol, triethylcitrate,

tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, and medium-chain triglycerides.

22. The composition according to any one of claims 1 to 21, wherein the layer containing a pH responding polymer further comprises a water soluble or swellable poreforming material.

23. The composition according to any one of claims 1 to 22, wherein the water soluble or swellable poreforming material is selected from the group consisting of HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, cellulose acetate phthalate, ammonio methacrylate copolymer, methacrylic acid copolymer, and mixtures thereof.

24. The composition according to any one of claims 1 to 23, wherein the composition comprises a layer containing a non-thermoplastic polymer.

25. The composition according to any one of claims 1 to 24, which comprises

Composition (mg)	**mg/Capsule**
2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine	1.3
Sugar spheres	162.9
HPMC	10.2
Ethyl cellulsoe Dispersion	8.9
Poly(meth)acrylate	9.1
Tri-ethyl citrate (TEC)	0.9
Talc	6.7
Total fill weight (mg) in a capsule	200.0
Hard Gelatin Capsules (Size #2)	61.0