ANTIPSYCHOTIC INJECTABLE DEPOT COMPOSITION

TECHNICAL FIELD

The present invention is related to implantable compositions for extended drug-delivery devices comprising certain atypical antipsychotic drugs, particularly risperidone. Specifically, the present invention is related to compositions for injectable *in-situ* forming biodegradable implants comprising risperidone.

BACKGROUND ART

Risperidone is an atypical antipsychotic drug with benzisoxazole and piperidine functional groups, which acts as strong dopaminergic antagonist and selective serotonin receptor antagonist. Risperidone is FDA approved for the treatment of schizophrenia since 1993. It is the only drug presently approved for the treatment of schizophrenia in young people under 18 years, and together with lithium, for the treatment of bipolar disorders in children/youth ages between 10-18 years old. Conventional risperidone therapy of schizophrenia involves daily oral tablets, although it is also available as a solution and orally disintegrating tablets.

In fact, one of the intrinsic problems that risperidone-targeted patients usually face is the dissociation of some schizophrenic patients from the treatment, moreover when it consists of a daily medication, leading to irregular or inconstant treatments and favouring the appearance of psychotic crisis. Moreover, this kind of therapy gives rise to high differences in the plasma levels (measured as the difference between Cmax and Cmin) in patients, therefore usually affecting the patient's mood.

Risperidone is therefore a good drug candidate for incorporation into sustained delivery devices, where the patients would be covered or treated for long time periods with just one dose and without the need of caregivers to pay attention to a daily medication, and where more homogeneous plasma levels in the patient are desirable.

One of the most usual ways to administer risperidone presently is through the use of depot injections. Depot injections allow careful control of drug usage (as opposed to orally administered drugs) and ensure regular contact between the caregivers team and the patient, where overall treatment efficacy and/or side effects may be identified. Furthermore, it is easy to identify defaulters and prepare interventions. However, *in situ* forming implants currently described in the state of the art cannot properly control risperidone release from the implant, and fail to allow obtaining therapeutic plasma levels in a bi-weekly administration protocol, with reasonable differences between maximum and minimum concentrations.

Currently, the long-acting injectable risperidone formulation, Risperdal Consta®, is the first depot atypical antipsychotic drug in the market. It is an intramuscular risperidone-containing PLGA microparticles formulation and is intended to deliver therapeutic levels of risperidone by bi-weekly administrations. However, due to the inherent lag phase of most microparticle based products, the patient is required to supplement the first weeks with daily doses of oral risperidone after first administration. Approximately three weeks after a single intramuscular injection of Risperdal Consta® and concurrent daily doses of oral risperidone, the microspheres release sufficient risperidone in the systemic circulation that the patient can discontinue supplementation with daily doses of the oral therapy. However, this period of oral supplementation could be a risk factor of non-compliance. Also, the presence on the body of two doses at the same time could be a potential risk of adverse events, such as irregular formulation behaviour and toxicity.

The risperidone compositions of the invention, on the contrary, can evoke therapeutic drug plasma levels from the first day up to at least 14 days, avoiding the need of supplementary oral daily therapy from the administration moment. These compositions can also reduce the differences between Cmax and Cmin as observed with daily-administered oral tablets and subsequently may reduce variations in the patient mood. In addition, they can also cover a period within administrations that is at least as long as the period covered by currently marketed extended-release risperidone formulations.

The compositions of the invention are based on a biodegradable copolymer poly(L-lactide-co-glycolide) matrix. These polymers have been used for many years in medical applications like sutures described in US 3,636,956 by Schneider, surgical clips and staples described in US 4,523,591 by Kaplan et al., and drug delivery systems described in US 3,773,919 by Boswell et al. However, most of the existing formulations using these biodegradable polymers require manufacturing of an implantable device in solid form prior to the administration into the body, which device is then inserted through an incision or is suspended in a vehicle and then injected. In such instances, the drug is incorporated into the polymer and the mixture is shaped into a certain form such as a cylinder, disc, or fibre for implantation. With such solid implants, the drug delivery system has to be inserted into the body through an incision. These incisions are sometimes larger than desired by the medical profession and occasionally lead to a reluctance of the patients to accept such an implant or drug delivery system.

Injectable biodegradable polymeric matrix implants based on lactic acid, glycolic acid and/or their copolymers for sustained release have already been described in the state of the art. For instance, US 5,620,700 issued to Berggren describes a bioerodible oligomer or polymer material containing drug for local application into a diseased tissue pocket such as a periodontal pocket. However, the material requires heating to high temperatures to become sufficiently flowable to allow the injection, so that hardening of the material after cooling to the body temperature conforms the implant.

US 6,673,767 issued to Brodbeck describes procedures to obtain *in situ* forming biodegradable implants by using biocompatible polymers and biocompatible low water-miscible solvents. According to this document, a viscous polymeric solution containing the drug that upon injection releases the drug in a controlled manner can be obtained through the use of low water-soluble solvents. In this document, low water-soluble solvents (less than 7% miscibility in water) are used as a method to reduce the release of the drug in aqueous mediums, allowing initial drug releases of 10% or lower during the first 24 hours. However, in our experience, the use of water-immiscible and/or low water-miscible solvents cannot satisfactorily control the initial *in vivo* release of

risperidone during the first 24 hours. For example, the use of benzyl alcohol, a solvent specifically included in US 6,673,767, causes very high plasma levels of risperidone in the first 3 days and then the plasma levels decrease to very low levels in 7 days, whereas the use of N-methyl pyrrolidone, a solvent with a much higher water solubility, provides much smaller initial plasma levels of risperidone and therefore a better control of the release of the drug during the first 5 days after the injection. This effect on the release of risperidone is completely unexpected from US 6,673,767.

US 6,331,311, again issued to Brodbeck, also discloses injectable depot compositions comprising a biocompatible polymer such as PLGA, a solvent such as N-methyl-2-pyrrolidone and a beneficial agent such as a drug, further comprising an emulsifying agent such as polyols. However, the compositions disclosed do not perform satisfactorily when the beneficial agent is risperidone because the use of a two-phase composition with emulsifying agents accelerates implant hydration and increases effective releasing surface area, impairing the control on the initial burst release and originating a fast decrease in drug release from the first days to the following ones.

US 4,938,763, issued to Dunn et al., discloses a method for an injectable *in situ* forming implant. A biodegradable polymer or copolymer dissolved in a water-miscible solvent with a biologically active agent either is dissolved or dispersed within the polymeric solution. Once the polymeric solution is exposed to body fluids, the solvent diffuses and polymer solidifies entrapping the drug within the polymer matrix. Even though patent 4,938,763 discloses the use of water miscible solvents for obtaining *in situ* forming polymeric implants, however this document discloses a number of polymers and solvents and even proportions between the different ingredients that do not produce a satisfactory implant with the appropriate release characteristics, particularly when the implant contains risperidone as active principle.

Another way to avoid surgery to administer these drugs is the injection of small-sized polymeric particles, microspheres or microparticles containing the respective drug. For instance, US 4,389,330 and US 4,530,840 describe a method for the preparation of

biodegradable microparticles. US 5,688,801 and US 6,803,055 are related to the microencapsulation of 1,2-benzazoles into polymeric particles to achieve a drug release over extended periods of time in the treatment of mental disorders. These microparticles require re-suspension into aqueous solvents prior to the injection. On the contrary, the compositions of the invention are injected as a liquid or semisolid formulations that precipitate by solvent diffusion after the injection and forms a single (not multiparticulate) solid implant.

Based on these previous patents, US 5,770,231 describes a method for producing risperidone and 9-hydroxy-risperidone biodegradable microparticles for sustained release by dissolving the drug within an organic phase. However, the use of organic solvents that are able to dissolve the risperidone mostly or completely gives rise to very high initial plasma levels of risperidone due to the diffusion of the drug along with the diffusion of the solvent.

US 7,118,763 describes two methods of making multi-phase sustained-release microparticle formulations based on the combination of different particle sizes or microparticles exhibiting different release profiles. The combination of two different release profiles allows the release of the drug for periods longer than two weeks. However, in practice this combination requires a mixture of particles from at least two different batches, involving the multiplication of end product specifications and increasing batch-to-batch variability. On the contrary, the compositions of the invention provide an easier method for the production of a single unit implantable device allowing constant and effective plasma levels during a period comprising from the first day up to at least 14 days.

Finally, WO 2008/153611 A2 discloses a rather large amount of sustained delivery systems of risperidone compounds. However, the authors of this document failed to obtain the conclusions reached during the present work, so that the influence in the initial risperidone burst of certain parameters or ratios as presently disclosed was ignored. In particular, none of the formulations in this document contained a

CLAIMS

1. An injectable depot composition, comprising:

- a drug which is risperidone and/or 9-OH-risperidone in any combination thereof;
- at least a biocompatible polymer which is a copolymer based on lactic and glycolic acid having a monomer ratio of lactic to glycolic acid in the range from 50:50 to 75:25, and
- at least a water-miscible solvent with a dipole moment about 3.9-4.3 D,

wherein the viscosity of the solution comprising the polymer and the solvent is between 0.5 and 3.0 Pa.s and the solvent/drug mass ratio is between 10 and 4,
characterised in that the drug/polymer mass ratio is between 25 and 35% expressed as the weight percentage of the drug with respect of the drug plus polymer, and in that the composition further comprises $Mg(OH)_2$ in a molar ratio between 2/3 and 2/5, expressed as the molar ratio of drug to $Mg(OH)_2$.

2. The composition according to claim 1, wherein the solvent is dimethylsulfoxide (DMSO).

3. The composition according to claims 1 or 2, wherein the drug/polymer mass ratio is about 33%.

4. The composition according to any one of claims 1 to 3, wherein the solvent/drug mass ratio is between 5 and 4.

5. The composition according to claim 4, wherein the solvent/drug mass ratio is about 4.66.

6. The composition of any one of previous claims 1-5, wherein the particle size distribution of the drug is:

- less than 10% particles smaller than 10 microns;
- less than 10% particles larger than 225 microns, and
- a d0.5 value in the range of 60-130 microns.

7. The composition according to any one of the previous claims wherein the mass ratio between the weight of the solution comprising the polymer and the solvent and the drug is between 15 and 5.

8. The composition according to claim 7, wherein the mass ratio between the weight of the solution comprising the polymer and the solvent and the drug is between 12 and 5.

9. The composition according to claim 8, wherein the mass ratio between the weight of the solution comprising the polymer and the solvent and the drug is between 7 and 6,5.

10. The composition according to claim 9, wherein the mass ratio between the weight of the solution comprising the polymer and the solvent and the drug is about 6,66.

11. The composition according to claim 1, wherein the particle size of the $Mg(OH)_2$ is below 10 microns.

12. The composition of any one of the previous claims which is a sterile composition.

13. The composition of any one of previous claims for the treatment of schizophrenia or bipolar disorders in the human body.

14. A pharmaceutical kit suitable for the in situ formation of a biodegradable implant in a body comprising the composition of any one of claims 1-13, wherein the drug and the biocompatible polymer are contained in a first container, and the solvent is contained in a second, separate container.

15. The pharmaceutical kit according to claim 14, wherein at least one of the first and second containers is a syringe, a vial, a device or a cartridge, either disposable or not

16. The pharmaceutical kit according to claim 15, wherein both the first and the second containers are disposable syringes.

17. The pharmaceutical kit according to claim 16, wherein the syringes are connectable through a connector device or a direct thread.