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. Other forms of sustained release risperidone formulations exist. For example, WO2008/153611 A2 discloses risperidone sustained release delivery systems for the treatment of medical conditions relating delusional psychosis, schizophrenia, bipolar disorder, psychotic depression obsessive-compulsion disorder, Tourette syndrome and autistic spectrum disorders. Whereas US 2004/0247870 A1 discloses a method for preparing an injectable composition of microparticles for the sustained release of a biologically active agent.

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 accepts 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

risperidone/polymer mass ratio between 25 and 35%, as in the presently claimed formulations.Moreover, all the tests disclosed in D1 were carried out using a specific solvent, namely N-methyl-2-pyrrolidone (NMP).

In addition, although microparticle formulations can be administered by injection, they cannot always satisfy the demand for a biodegradable implant because they sometimes present difficulties in the large-scale production. Moreover, in case of any medical complication after injection, they are more problematic to be removed from the body than implantable compositions such as those of the invention.

SUMMARY OF THE INVENTION

Therefore, the compositions already described in the state of the art do not cover the existing needs in risperidone compositions, kits and treatments for psychiatric disorders, and there still exists a need of compositions and devices to allow a controlled, constant release of the drug during prolonged periods of time.

The solution is based on the fact that the present inventors have identified that the initial burst release of the drug can be satisfactorily controlled during at least 2 weeks by controlling at least one of the following factors, either alone or in combination:

- the viscosity of the polymeric solution. Throughout the present specification, by "polymeric solution" it is understood the combination of the polymer and the solvent where it is dissolved;
- the risperidone/polymer mass ratio,
- the risperidone particle size,
- the polymeric solution/drug mass ratio, and
- the solvent/risperidone mass ratio

By adequately controlling at least some of these factors, the release from the implant during at least the first two weeks can be precisely controlled, allowing satisfactory

release profiles from the very first day until at least 14 days, and achieving in some cases more than 30 days and up to 40 days following a single administration.

In the implantable compositions of the invention, compositions and kits are provided in which a solid polymer or copolymer is dissolved in a solvent, which is non-toxic and water miscible, to form a liquid solution, to which the risperidone is provided. When these compositions are exposed to body fluids or water, the solvent diffuses away from the polymer-drug mixture and water diffuses into the mixture where it coagulates the polymer thereby trapping or encapsulating the drug within the polymeric matrix as the implant solidifies. The release of the drug then follows the general rules for diffusion or dissolution of a drug from within a polymeric matrix. The risperidone compositions of the invention can therefore form a suspension or a dispersion within a biodegradable and biocompatible polymeric solution that can be administered by means of a syringe and a needle and which solidifies inside the body by solvent diffusion, thereby forming the implant.

The compositions of the invention comprise at least a polymer matrix, a solvent and a drug having certain selected ranges and ratios of at least one of the following parameters, either alone or in combination:

- the viscosity of the polymeric solution (polymer + solvent);
- the risperidone/polymer mass ratio,
- the risperidone particle size.

Additional parameters such as the mass ratio between the amounts of polymeric solution (polymer + solvent) and drug, and the solvent/drug mass ratio, can also be useful to control the initial release of the compositions of the invention.

Some of the key points where the compositions of the invention show improvements over the state of the art are:

- Stability, by using a solid product for reconstitution previous to injection;
- Pharmacokinetic profile:

  - Onset: The compositions of the invention show plasma therapeutic levels since the first day, avoiding the 2-3 weeks lag time that the currently marketed long-term risperidone product shows.
  - Duration: The compositions of the invention may allow an increase in the interval between administrations as compared to currently marketed long-term risperidone product.
- Levels: The compositions of the invention induce more sustained plasma levels, and with lower differences between Cmax and Cmin than the currently marketed long-term risperidone product.

Accordingly, a first aspect of the invention is directed to an injectable depot composition, comprising:

- a drug which is risperidone and/or its metabolites or prodrugs 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.

A second aspect of the invention is directed to the use of such compositions for the treatment of schizophrenia or bipolar disorders in the human body.

And a third aspect of the invention is directed to a pharmaceutical kit suitable for the *in situ* formation of a biodegradable implant in a body comprising the said compositions, wherein the risperidone drug and the biocompatible polymer are contained in a first container, and the water-miscible solvent is contained in a second, separate container. These containers may be syringes and the mixing of the contents of the first and second

containers may be performed by direct or indirect connection followed by moving forwards and backwards the plungers of the syringes.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention comprise at least a polymer or polymer matrix, a solvent and a drug.

The **polymer** or polymer matrix is preferably a biocompatible and biodegradable polymer matrix. In order not to cause any severe damage to the body following administration, the preferred polymers are biocompatible, non-toxic for the human body, not carcinogenic, and do not induce significant tissue inflammation. The polymers are preferably biodegradable in order to allow natural degradation by body processes, so that they are readily disposable and do not accumulate in the body. The preferred polymeric matrices in the practice in this invention are selected from end-capped terminal carboxylic poly-lactide and poly-glycolic acid copolymers mixed in a ratio from 50:50 to 75:25, with intrinsic inherent viscosity preferably in the range of 0.16-0.60 dl/g, and more preferably between 0.25-0.48 dl/g, measured in chloroform at 25°C and a 0.1% concentration. The concentration of the polymeric component in the compositions of the invention is preferably comprised in the range of 25-50%, (expressed as the percentage of polymer weight based on total polymeric solution component) and more preferably between 30-40%.

For the purpose of the present invention, throughout the present specification the term intrinsic or inherent viscosity (η_{inh}) of the polymer is defined as the ratio of the natural logarithm of the relative viscosity, η_r, to the mass concentration of the polymer, c, i.e.:

$$\eta_{inh} = (\ln \eta_r)/c$$

and the relative viscosity (η_r) is the ratio of the viscosity of the solution η to the viscosity of the solvent η_s, i.e.:

$\eta_r = \eta / \eta_s$

If not otherwise specified, the intrinsic viscosity values throughout the present specification are to be understood as measured at 25°C in chloroform at a concentration of 0.1%. The value of intrinsic viscosity is considered in the present specification, as commonly accepted in the art, as an indirect indicator of the polymer molecular weight. In this way, a reduction in the intrinsic viscosity of a polymer, measured at a given concentration in a certain solvent, with same monomer composition and terminal end groups, is an indication of a reduction in the polymer molecular weight (IUPAC. Basic definitions of terms relating to polymers 1974. Pure Appl. Chem. 40, 477-491 (1974).

The preferred **solvents** are non-toxic, biocompatible and appropriate for parenteral injection. Solvents susceptible of causing toxicity should not be used for the injection of any material into any living body. More preferably, selected solvents are biocompatible in order not to cause any severe tissue irritation or necrosis at the injection site. Therefore, the solvent is preferably classified as class II or III, and more preferably class III, according to ICH Guidelines. For the formation of the *in-situ* implant, the solvent should preferably diffuse quickly from the polymeric solution towards surrounding tissues when is exposed to physiological fluids. Consequently, the solvent is preferably water miscible and more preferably with a dipole moment about 3.9-4.3 D at 25°C. The most preferred solvents are DMSO, N-methyl-pyrrolidone and PEG.

The **drug** is preferably risperidone and/or a metabolite or a prodrug thereof. This drug is preferably at least partly suspended in the solvent. The solubility of the drug in the solvent is preferably lower than 90 mg/ml, more preferably lower than 65 mg/ml, and most preferably below 10 mg/ml. The advantage of this low solubility is that the initial burst of the drug when the solvent diffuses to the external aqueous medium is greatly reduced. In addition, in the final compositions of the invention the drug is provided in a preferred concentration between 4 and 16 wt%, expressed as the percentage of the drug in respect of the total composition weight. More preferably, the drug content is between 7 and 15%, and most preferably about 13% in respect of the total composition weight.

One of the factors contributing to control the initial release of the composition of the invention is the viscosity of the polymeric solution. The "polymeric solution", which is defined as the combination of the polymer matrix and the solvent where it is dissolved, has a preferred viscosity in the range of 0.5-7.0 Pa.s, more preferably between 0.5-3.0 Pa.s, and most preferably about 0.7-3.0 Pa.s.

A second factor contributing to control the initial release of the compositions of the invention is the risperidone/polymer mass ratio. The preferable ranges for this mass ratio, expressed as the percentage of the drug weight in respect of the drug plus polymer weight content, should be in a range of 15-40% weight, more preferably 25-35%, and most preferably about 33%.

A third factor contributing to control the initial release of the compositions of the invention is the drug's particle size. Large particles provide a smaller surface area per weight thereby reducing the initial release (burst) but the release may be then delayed until the beginning of the degradation of the polymeric matrix. On the other hand, small particles evoke higher burst levels due to an easier drug diffusion from small particles during implant hardening, followed by continuous drug release levels due to the combination of the processes of drug diffusion and implant erosion. Consequently, in a preferred embodiment of the invention a wide particle size distribution, combining large and small particle sizes in different ratios, is used in order to reduce the initial burst and maintain a constant drug release by diffusion of smaller particles on first phase and gradually releasing bigger particles while the polymer degrades. For instance, a preferred particle size distribution is as follows: not more than 10% of the total volume of particles in particles having a less than 10 microns size and not more of 10% of the total volume of particles in particles having a higher than 225 microns size. In addition, the d0.5 value is preferably in the range of 60-130 microns.

In addition to the above factors, the following ratios between the components of the compositions according to the invention can also contribute to control the initial release:

The mass ratio between the amounts of polymeric solution (polymer + solvent) and risperidone in the compositions of the invention is preferably between 15 to 5, more preferably between 12 to 5 and most preferably between 7 and 6.5. In most preferred embodiments this mass ratio is about 6.66, as shown in the Examples below (see Example 12).

The mass ratio between the amounts of solvent and risperidone (mg solvent/mg risperidone) in the compositions of the invention is preferably between 12 to 4, more preferably between 10 to 4 and most preferably between 5 and 4. In most preferred embodiments this mass ratio is about 4.66 (see Example 13 below). This ratio defines the rate of hardening of the implant by solvent diffusion and consequently the precipitation of the polymer. Hence, this parameter is also related to the proportion of drug dissolved/dispersed in the polymeric solution and therefore it controls whether further drug is diffused from the implant or not.

Optionally, an alkaline agent with low water solubility such as lower than 0.02 mg/ml can be included within the polymer matrix, preferably in a molar relation >2/5 (drug/alkaline agent). Preferred alkalinising agents are alkaline or alkaline-earth hydroxides such as magnesium hydroxide. Preferably, the particle size of the magnesium hydroxide is below 10 microns.

Another aspect of the invention is directed to a kit comprising a first container, preferably syringes, vials, devices or cartridges, all of them either being disposable or not, containing a polymer in solid form, preferably freeze-dried, such as PLGA and risperidone (either or not additionally containing $Mg(OH)_2$) in the appropriate amounts and a second container, likewise preferably syringes, vials, devices or cartridges, all of them being either disposable or not, containing the water-miscible solvent. When required, the contents of both containers are combined, for example through a connector or by using male-female syringes, and mixed each other so that the compositions according to the invention are reconstituted, for example by moving forwards and

backwards the plungers of the syringes. Illustrative preferred embodiments are shown in Figure 35 (syringes connected through a connector device) and in Figure 36 (syringes connected through a direct thread).

In a preferred embodiment, the injectable depot compositions of the invention further comprise $Mg(OH)_2$ at a molar ratio between 2/3 and 2/5, expressed as the molar ratio of drug to $Mg(OH)_2$.

In an additional preferred embodiment, the injectable depot composition is sterile as a finished product. In other preferred embodiment, the biocompatible polymer is sterilized previously to its aseptic filling process, preferably by an aseptic filling process by irradation in the range 5-25 KGy. In yet another embodiment, the biocompatible polymer is sterilized previously dissolved in a solvent by a filtration process in a filter with a 0.22 μm pore size.

In another preferred embodiment, in the injectable depot composition at least the drug and/or the biocompatible polymer of the composition have been submitted to terminal sterilization processes, preferably by irradiation in the range 5-25 KGy.

BRIEF DESCRIPTION OF THE FIGURES

Fig 1: *In vitro* release profile of risperidone for the composition of Comparative Example 1 (risperidone, polymer and a water-insoluble solvent).

Fig. 2: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the composition of Comparative Example 1 (risperidone, polymer and a water-insoluble solvent) in rabbits.

Fig. 3: *In vitro* release profile of risperidone for the composition of Example 1 (risperidone, polymer and water-soluble solvents having different dipole moment).

Fig. 4: *In vitro* release profile of risperidone for the composition of Example 2 (risperidone, polymer and a water-soluble solvent having a high solubility for risperidone).

Fig. 5: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the composition of Example 2 (risperidone, polymer and a water-soluble solvent having a high solubility for risperidone) in rabbits.

Fig. 6: *In vitro* release profile of risperidone for the composition of Example 3 (risperidone, polymer and water-soluble solvents having moderate to low solubility for risperidone).

Fig. 7: *In vitro* release profile of risperidone for the compositions of Example 4 (different polymer concentrations with respect to solvent).

Fig. 8: *In vitro* release profile of risperidone for the compositions of Example 5 (low polymer concentration of a solvent having a high solubility for risperidone).

Fig. 9: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the composition of Example 5 (low polymer concentration of a solvent having a high solubility for risperidone) in rabbits.

Fig. 10: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the composition of Example 6 (intermediate polymer concentration with respect to solvent) in rabbits.

Fig. 11: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 7 (different drug loadings) in rabbits.

Fig. 12: *In vitro* release profile of risperidone for Composition B of Example 8 (different particle sizes).

Fig. 13: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of Composition A of Example 8 (different particle sizes) in rabbits.

Fig. 14: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of Composition B of Example 8 (different particle sizes) in rabbits.

Fig. 15: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of Composition B of Example 8 (different particle sizes) in dogs.

Fig. 16: *In vitro* release profile of risperidone for the compositions of Example 9 (different viscosities of the polymeric solution).

Fig. 17: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 9 (different viscosities of the polymeric solution) in rabbits.

Fig. 18: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 9 (different viscosities of the polymeric solution) in rabbits.

Fig. 19: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 9 (different viscosities of the polymeric solution) in rabbits.

Fig 20: *In vitro* release profile of risperidone for the compositions of Example 10 (different drug/polymer mass ratios in DMSO as solvent).

Fig. 21: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions Example 10 (different drug/polymer mass ratios) in rabbits.

Fig. 22: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions Example 10 (different drug/polymer mass ratios) in rabbits.

Fig. 23: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions Example 10 (different drug/polymer mass ratios) in dogs.

Fig. 24: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions Example 11 (different polymeric solution/drug mass ratios) in rabbits.

Fig. 25: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions Example 12 (different solvent/drug mass ratios) in rabbits.

Fig. 26: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions Example 13 (optional addition of $Mg(OH)_2$) in rabbits.

Fig 27: *In vitro* release profile of risperidone for the compositions of Example 14 (different reconstitution methods).

Fig. 28: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 14 (different reconstitution methods) in rabbits.

Fig. 29: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 14 (different reconstitution methods) in dogs.

Fig 30: *In vitro* release profile of risperidone for the compositions of Example 15 (sterilization by irradiation).

Fig 31: *In vitro* release profile of risperidone for the compositions of Example 15 (sterilization by irradiation).

Fig. 32: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 15 (sterilization by irradiation) in rabbits.

Fig. 33: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Example 15 (sterilization by irradiation) in rabbits.

Fig. 34: *In vivo* plasma levels of risperidone plus 9-OH-risperidone following injection of the compositions of Comparative Example 2 (compositions obtained through the procedures of the prior art) in dogs.

EXAMPLES

The following examples illustrate the invention and should not be considered in a limitative sense thereof.

In the sense of the present invention, without limitation and in connection with the *in vivo* examples, for "Initial Burst" or initial release it is meant the addition of the plasma levels of risperidone plus those of 9-OH-risperidone, which addition is also called "the active moiety" throughout the present specification, from the moment of the injection until the third day after the administration. Also in the sense of this invention, without limitation and in connection with the examples, acceptable plasma levels of active moiety during the initial burst phase are below 100 ng/ml in Beagle dogs and New Zealand White Rabbits when doses administered are 2,5 mg/kg risperidone in dogs and 5 mg/kg risperidone in rabbits.

Comparative Example 1: Implantable composition including a water-insoluble solvent (example not according to the invention).

In the present example, the composition of the implantable formulation was as follows:

Ingredient	Amount (mg)
Resomer®RG752S (polymer)	100
Risperidone	25
Benzyl benzoate (solvent)	233.3

RG752S, 75:25 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone implantable formulation was prepared by completely dissolving the polymer in the solvent and subsequently suspending the drug in said polymeric solution.

In vitro release profile:

The risperidone release from the formulation of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks having a pre-warmed release medium by using a 21G needle. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, 3d, 6d, 8d, 10d, 13d, 17d, 21d, 23d, 28d, 31d, 35d, 42d), 5 ml of release medium was collected and replaced with fresh buffer and the amount of risperidone present in the sample was determined by UV spectrophotometry. The profile of risperidone released from the implants of this example is shown in Figure 1. The results are expressed as % Risperidone released from implants as a function of time.

As it can be observed in this Figure 1, the release of risperidone during the first 24 hours is close to 20% of the injected amount and close to 50% in the first 48 hours. This finding is not in accordance with previous teachings such as US 6,673,767, since this low water-miscible solvent is clearly unable to control the initial diffusion of risperidone from the polymer matrix.

In vivo plasma levels after intramuscular administration to New Zealand rabbit:

The risperidone composition of this example was intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d and 28d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the plasma levels of the risperidone active moiety is shown in Figure 2. The results are expressed as the addition of risperidone plus 9-OH-risperidone concentrations (ng/ml) as the function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in this Figure, the injection of an amount of composition equivalent to 15 mg risperidone to New Zealand White rabbits resulted in very high initial plasma levels followed by a rapid decrease, with no significant plasma levels from day 3 onwards. All 3 animals exhibited severe adverse effects related to the very high plasma levels of risperidone active moiety 15 min after the injection, which demonstrates the rather poor control on the initial drug release achieved with this composition.

Example 1: Study of different water-soluble solvents with different dipole moment.

In the present example, the composition of the implantable formulation was as follows:

Ingredient	Composition 1	Composition 2	Solvent dipole moment (D)
	Amount (mg)		
Resomer®RG503 (polymer)	100	100	
Risperidone	25	25	
Dimethyl sulfoxide (solvent)	233.3	--	3.96
1,4 –dioxane (solvent)	--	233.3	0.45

RG503, 50:50 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone-implantable formulation was prepared by completely dissolving the polymer in either of the cited water-miscible solvents having different dipole moment (DMSO or 1,4-dioxane) and subsequently suspending the drug in said polymeric solution.

In vitro release profile:

The risperidone release from the formulations of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, 3d, 6d, 8d, 10d, 13d, 17d, 21d, 23d, 28d, 31d, 35d, 42d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone amount present in the sample was determined by UV spectrophotometry.

The profile of the risperidone released from the formulations is shown in Figure 3. The results are expressed as %Risperidone released from the implants as a function of time. As it can be observed in this Figure 3, and in comparison with Figure 1 (corresponding to Comparative Example 1), the use of water miscible solvents versus water-inmiscible solvents in the implantable compositions of the invention allows a more precise control of the initial risperidone diffusion from the polymer matrix. The present example also shows the influence of the dipole moment of the solvent in the release of risperidone from the implantable compositions of the invention: The use of solvents with lower dipole moment (dioxane) causes a higher risperidone diffusion than solvents having higher dipole moment solvents (DMSO) about 3.9-4.3 D, which solvents notably reduce the drug diffusion during 2 weeks.

Example 2: Study of solvents with a high solubility for risperidone:

In the present example, the composition of the implantable formulation was as follows:

Ingredient	Amount (mg)
Resomer®RG752S (polymer)	100
Risperidone	25
Benzyl alcohol (solvent)	233.3

RG752S, 75:25 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone-implantable formulation of this example was prepared by completely dissolving the polymer in the water-miscible solvent having a high solubility for risperidone (benzyl alcohol) and subsequently suspending the drug in said polymeric solution.

In vitro release profile:

The risperidone release from the formulation of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks having a pre-warmed release medium by using a 21G needle. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, 3d, 6d, 8d, 10d, 13d, 17d, 21d, 23d, 28d, 31d, 35d, 42d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the formulation is shown in Figure 4. The results are expressed as %Risperidone released from the implants as a function of time. As it can be observed in Figure 4, the use of solvents having a high solubility for risperidone as in the present example results in a high initial risperidone diffusion and a

drug release from the polymer matrix close to 30% in the first 3 days and along the first week.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone composition of this example was intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d and 28d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 5. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as the function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in the cited Figure, the injection of the tested composition in an amount equivalent to 15 mg risperidone to New Zealand White rabbits resulted in very high initial plasma levels followed by a rapid decrease, with no significant plasma levels from day 5 onwards. All 3 animals exhibited adverse effects related to the very high plasma levels of risperidone active moiety 15 min after the injection, which demonstrates the very poor control on the initial drug release achieved with this composition, which comprises a solvent having a high solubility for risperidone.

Example 3: Study of solvents with different solubility for risperidone:

In the present case, the risperidone implantable formulation was prepared by completely dissolving polymer Resomer®RG503 (RG503, 50:50 lactic/glycolic acid, Boehringer Ingelheim) in different solvents (NMP, PEG and DMSO) having intermediate to low

solubility (in all cases below 65 mg/ml) for risperidone and subsequently suspending the risperidone in the respective solvent.

In vitro release profile:

The risperidone release from the formulations of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by the careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, 3d, 6d, 8d, 10d, 13d, 17d, 21d, 23d, 28d, 31d, 35d, 42d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the formulations is shown in Figure 6. The results are expressed as %Risperidone released from the formulations as a function of time. As it can be observed in Figure 6, the use of a solvent having a lower risperidone solubility (in comparison to high solubility as in Figure 4 from Example 2) offers initial controlled risperidone diffusion from the polymer matrix and a controlled release up to at least 28 days. Hence, the use of solvents having a low solubility for risperidone, such as DMSO, as in the present example, allows a more precise control of the drug released during the solvent diffusion and the polymer precipitation.

Example 4: Study of different polymer concentrations with respect to the solvent

In the present example, the compositions of the implantable formulations were as follows:

	Composition 1	Composition 2	Composition 3	Composition 4
Ingredient	Amount (%)			
Resomer®RG503 (polymer)	10	20	30	40
Dimethyl sulfoxide (solvent)	90	80	70	60

RG503, 50:50 lactic/glycolic acid (Boehringer Ingelheim)

The risperidone-implantable formulations were prepared by completely dissolving the polymer in the solvent in different proportions and subsequently suspending the drug in said polymeric solution.

In vitro release profile:

The risperidone release from the formulations of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by the careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer at pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, 3d, 6d, 8d, 10d, 13d, 17d, 21d, 23d, 28d, 31d, 35d, 42d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the formulations of this example is shown in Figure 7. The results are expressed as %Risperidone released from the formulations as a function of time. As it can be observed in Figure 7, the use of polymer matrix solutions having a low polymer concentration (10% w/w), produces an extremely high initial risperidone release, so that the control of risperidone diffusion is very difficult. Although an increase in the polymer concentration to 20% (w/w) notably improves the

capacity to control the risperidone released from the polymer matrix, it is still not enough to completely control the initial risperidone diffusion release, which is close to 15% during first 24 hours. Polymer concentrations at 30 and 40% (w/w) lead to an efficient initial drug release control, achieving controlled release profiles up to 35-42 days.

Example 5: Study of a low (10%) polymer concentration with respect of the solvent, where the solvent has a very high solubility for risperidone.

In the present example, the composition of the implantable formulation was as follows:

Ingredient	Amount (mg)
Resomer®RG752S (polymer)	100
Risperidone	25
Benzyl alcohol (solvent)	900

RG752S, 75:25 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone-implantable formulation was prepared by completely dissolving the polymer in a solvent having a very high solubility for risperidone (benzyl alcohol) and subsequently suspending the drug in said polymeric solution. The concentration of the polymer with respect to the solvent was low (10%).

In vitro release profile:

The risperidone release from the formulation of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks having a pre-warmed release medium by using a 21G needle. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, 3d, 6d, 8d, 10d, 13d, 17d, 21d, 23d, 28d, 31d, 35d, 42d), 5 ml of release medium was collected and replaced with fresh

buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the implants is shown in Figure 8. The results are expressed as %Risperidone released from the formulation as a function of time. As it can be observed in Figure 8, and in line with the results shown in Figure 7 from Example 4, a concentration of the polymer of 10% (w/w) in the polymeric solution is not enough to retain the risperidone in the implantable formulations, therefore inducing a too high initial risperidone diffusion during the first days.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone composition was intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d and 28d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 9. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in said Figure, the injection of an amount of formulation equivalent to 15 mg risperidone to New Zealand White rabbits resulted in very high initial plasma levels released, followed by a rapid decrease, with no significant plasma levels from day 5 onwards. All 3 animals exhibited adverse effects related to the very high plasma levels of risperidone active moiety 15 min after the injection, which shows a very poor control

on the initial drug release achieved with this composition comprising low polymer concentration in the polymer matrix.

Example 6: Study of intermediate (25%) polymer concentrations with respect of solvent.

In the present example, the compositions of the implantable formulation were as follows:

Ingredient	Amount (mg)
Resomer®RG503 (polymer)	41.7
Risperidone	25
Polyethylene glycol 300 (solvent)	125

RG503, 50:50 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone-implantable formulations were prepared by completely dissolving the polymer in the solvent and subsequently suspending the drug in said polymeric solution. The concentration of the polymer with respect to the solvent was intermediate (25%).

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone composition was intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown

in Figure 10. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed from the cited Figure, the injection of an amount of formulation equivalent to 15 mg risperidone to New Zealand White rabbits resulted in moderate initial plasma levels followed by a decrease until day 2 and sustained plasma levels at least up to 24 days. The results obtained in this example are in accordance with those from Example 4, where polymer concentrations of 20% (w/w) or higher with respect to the polymeric solution are able to control the initial risperidone diffusion and achieve prolonged release over time.

Example 7: Study of different drug loadings

The risperidone implantable formulation of this example was prepared by completely dissolving polymer Resomer®RG503 (RG503, 50:50 lactic/glycolic acid, Boehringer Ingelheim) in DMSO and subsequently dispersing the drug in the appropriate amount to obtain a final drug loading between 7-13% (w/w) (weight of risperidone in respect of the total composition weight).

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone formulation of this example was intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 11. The results are expressed as the addition of the risperidone plus 9-OH-

risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in said Figure, the injection of an amount of composition equivalent to 15 mg risperidone to New Zealand White rabbits resulted in moderate and controlled initial plasma levels. An increase in the drug loading is related to a lower initial drug diffusion and release, producing as a result a decrease in the initial plasma levels. Therefore, a high drug loading is preferable for the case of long-term formulations, in order to achieve better balanced plasma levels in the whole drug release period. In general terms, a preferred range for the drug loading is between 4 and 16%, and a more preferred range is between 7 and 13%, expressed as the weight percent of drug with respect to the total composition.

Example 8: Study of different particle sizes.

In the present example, the following compositions of implantable formulations according to the invention were tested:

Composition A:

Ingredient	Amount (mg)
Resomer®RG503 (polymer)	100
Risperidone	25
Dimethyl sulfoxide (solvent)	233.3

Composition B:

Ingredient	Amount (mg)
Resomer®RG503 (polymer)	50
Risperidone	25
Dimethyl sulfoxide (solvent)	166.7

RG503, 50:50 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone-implantable formulations were prepared by completely dissolving the polymer in the solvent and subsequently suspending the drug in said polymeric solution.

The following different risperidone particle size distributions were evaluated for the same formulation:

- 25-350 microns: d0.1, 25 microns and d0.9, 350 microns (not more than 10% of drug particles with a particle size smaller than 25 microns, and not more than 10% particles larger than 350 microns).
- 25-225 microns: d0.1 of 25 microns and d0.9 of 225 microns (not more than 10% of drug particles with a particle size smaller than 25 microns, and not more than 10% particles larger than 225 microns).
- 90-150 microns: sieved between 90-150 microns
- 45-90 microns: sieved between 45-90 microns
- milled, <10 microns: drug milled to d0.9 10 microns (not more than 10% particles larger than 10 microns).

In vitro release profile:

The risperidone release from the formulations corresponding to Composition B was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by the careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, and periodically up to a maximum of 35d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the implants of this example is shown in Figure 12. Results are expressed as %Risperidone released from the implants as a function of time. As it can be observed in Figure 12, the small drug particles (less than 10 microns) favoured the *in vitro* drug diffusion during first days following administration of the

implantable formulation, whereas the use of a mixture of particle sizes, comprising larger and smaller particles, reduced the initial diffusion.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone formulations corresponding to Compositions A and B of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figures 13 and 14 for Compositions A and B, respectively. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in said Figures, the injection of an amount of formulation of the Compositions A and B corresponding to an equivalent to 15 mg risperidone to New Zealand White rabbits resulted in moderate and controlled initial plasma levels followed by significant plasma levels up to at least 21 days. The smaller particle sizes produce an initial raise in the plasma levels and shortens the therapeutic plasma levels window. The use of higher particle sizes, thus avoiding smaller ones, resulted in a dramatic reduction of the initial burst effect by decreasing drug diffusion, and the consequently delay on drug release until the polymer matrix degrades. As it is shown in Figure 14, the use of a controlled mixture of drug particle sizes induced a more controlled initial release during the diffusion phase, followed by an increase in plasma levels once the polymer degradation begins.

In vivo plasma levels after intramuscular administration to Beagle dog

The risperidone formulations of Composition B of this example were intramuscularly injected to Beagle dogs weighing an average of 10 kg. The amount injected corresponded to a dose of 25 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of dogs was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 15. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone.

The injection of risperidone formulations corresponding to Composition B of this example in an amount equivalent to 25 mg risperidone to Beagle dogs resulted in controlled initial plasma levels followed by significant plasma levels up to at least 28 days as it can be observed in Figure 15. As previously noted in relation to the intramuscular administration of Composition B to rabbits (Figures 13 and 14), the administration of the same composition to dogs revealed the same variable effect depending on drug particle size: Small particles (<10 microns) induced higher initial plasma levels and a relatively fast decrease in comparison with mixtures of particles sizes comprising both small and large particles (25-225 microns), which combination is able to reduce the initial plasma levels and favours a more sustained plasma level along time.

Example 9: Study of the viscosity of the polymeric solution:

The risperidone-implantable formulations of this example were prepared by completely dissolving the polymer in DMSO or NMP as the solvent and subsequently suspending

the drug in said polymeric solution. The formulations were the following in order to achieve polymeric solutions having different viscosities:

Polymer Type	Polymer (%)	Viscosity of the polymeric solution (Pa.s)
Resomer®RG503	10	0.03
Resomer®RG752S	30	0.10
Resomer®RG503	20	0.18
Resomer®RG752S	40	0.43
Resomer®RG753S	30	0.66
Resomer®RG503	30	1.12
Resomer®RG503	35	2.73
Resomer®RG504	30	6.12
Resomer®RG503	40	6.77

RG752S, and RG753S, 75:25 lactic/glycolic acid polymer (Boehringer Ingelheim)

RG503 and RG504, 50:50 lactic/glycolic acid polymer (Boehringer Ingelheim)

In vitro release profile:

The risperidone release from the formulations was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by the careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, and periodically up to a maximum of 42d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the implants of this example is shown in Figure 16. Results are expressed as %Risperidone released from the implants as a function of time. As it can be observed in Figure 16, the low polymer solution viscosities lead to completely uncontrollable (0.03 Pa.s) and fast and high initial diffusion (0.18 Pa.s) of

risperidone. On the other hand, polymer solution viscosities in the range 1.12-6.77 Pa.s resulted in well-controlled *in vitro* drug diffusion during first days following administration of the implantable formulation, followed by moderate drug release rates up to 35-42 days.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone compositions of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figures 17, 18 and 19. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in said Figures, the injection of an amount of formulation corresponding to 15 mg risperidone to New Zealand White rabbits with compositions having a low viscosity (0.1 Pa.s) of the polymeric solution resulted in high initial plasma levels but a fast decrease of said levels. An intermediate polymer solution viscosity (0.43 Pa.s).still evokes high initial plasma levels, although their decrease is more moderate than at lower viscosity. On the contrary, higher viscosity of the polymeric solutions resulted in controlled initial plasma levels followed by significant plasma levels up at least 21 days when viscosity is over 0.5 Pa.s. In general terms, a preferred range for the viscosity of the polymer solution is between 0.5 and 7.0 Pa.s, and a more preferred range between 0.7 and 2.0 Pa.s.

Example 10: Study of different drug/polymer mass ratios

Risperidone implantable formulations were prepared by completely dissolving polymer Resomer®RG503 in the solvent and subsequently dispersing the drug in the appropriate amounts to obtain the following drug/polymer mass ratios, expressed as the percentage of risperidone weight in respect of the polymer + risperidone weight:

Risperidone/Polymer mass ratio [Risperidone/(Polymer+Risperidone) (%w/w)]							
15.0	20.0	25.0	30.0	33.3	35.0	37.5	40.0

In vitro release profile:

The risperidone release from some of the formulations of this example was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by the careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, and periodically up to a maximum of 42d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the formulations is shown in Figure 20. The results are expressed as %Risperidone released from the formulation as a function of time. . The range for the risperidone/polymer ratio between 15-35% presented in this example shows acceptable *in vitro* initial risperidone diffusion and a release time longer than 28 days. On the other hand, ratios of the order of 40% showed an inadequate control of the *in vitro* drug release, probably because the amount of polymer present in the composition was not enough for the proper risperidone entrapment into the matrix.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

Some of the risperidone compositions of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figures 21 and 22. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in the cited Figures, the injection of an amount of formulation corresponding to 15 mg risperidone to New Zealand White rabbits resulted in all the cases presented in this example to show plasma levels from the first day until at least day 24. However, in some cases, compositions resulted in moderate and well controlled initial plasma followed by sustained levels during 24 days, there being no high difference between that initial plasma levels (first day) and the ones found on the next days. Whereas in other cases, the compositions resulted in inadequately controlled initial plasma levels, showing high plasma levels during first day followed by a notably decrease during next days until plasma levels were stabilized and maintained until drug it is completely released. These finding resulted highly surprising, since what it could anticipated is that the lower drug/polymer mass ratio, the better control of the initial release due to a higher presence of polymer to entrap and retain the drug. However, what we found here, is that ratios lower than 25% could not elicit an appropriate risperidone release and showed a high diffusion from the compositions during the initial term following administration. On the other hand, ratios in the interval 25-35% were capable to evoke more sustained plasma levels since the very beginning with lower differences between initial levels (first day) and following ones (next days).Finally, an increase in the ratio over 35% resulted in higher initial plasma levels compared to ones obtained during the next days, so that a value of 35% in this ratio is considered to

represent a limit for the minimum amount of polymer which is necessary to provide a good risperidone entrapment into the composition matrix. In general terms, a preferred range for the risperidone/polymer mass ratio is between 25 and 35%. A most preferred value is around 33%.

In vivo plasma levels after intramuscular administration to Beagle dog

The risperidone formulations of this example corresponding to drug/polymer mass ratios of 20 and 33.3% were intramuscularly injected to Beagle dogs weighing an average of 10 kg. The amount injected corresponded to a dose of 25 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of dogs was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 23. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be seen in the cited Figure, the injection of an amount of formulation corresponding to 25 mg risperidone to Beagle dogs resulted in well-controlled initial plasma levels with sustained levels up to at least 35 days. And as previously described for rabbits, a higher drug/polymer mass ratio, between 25-35%, resulted in a surprisingly better control of the drug release than lower ones (below 25%), thus providing a controlled initial diffusion followed by a more constant release, so that more balanced plasma levels are obtained.

Example 11: Study of different polymeric solution/drug mass ratios

The risperidone implantable formulations of this example were prepared by completely dissolving polymer Resomer®RG503 (RG503, 50:50 lactic/glycolic acid, Boehringer

Ingelheim) in dimethyl sulfoxide and subsequently dispersing the drug in the mentioned polymeric solution adjusted to different polymeric solution/risperidone mass ratios (w/w): 6.7, 10, 11.4, 14 and 19, expressed as the weight percent of polymer solution with respect to drug.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone composition of this example was intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 2. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 24. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As shown in the cited Figure, the injection of an amount of formulation corresponding to 15 mg risperidone to New Zealand White rabbits resulted in well-controlled initial plasma levels 4h post-administration, which plasma levels were maintained up to 28 days in all polymeric solution/risperidone cases, although the lower the polymeric solution/risperidone ratio, the more constant levels were achieved. However the value of 19 is not considered adequate due to being capable to control the very initial release (and plasma levels) approximately during the first 24h, but not during the following days (from day 2^{nd} to 5^{th}). Therefore, an appropriate composition should present a polymer solution/drug mass ratio below 15 and at least until the last value tested (4).

Example 12: Study of different solvent/drug ratios.

Risperidone implantable formulations were prepared by completely dissolving polymer Resomer®RG503 (RG503, 50:50 lactic/glycolic acid, Boehringer Ingelheim) in dimethyl sulfoxide and subsequently dispersing the drug in the mentioned polymeric solution adjusted to different solvent/risperidone ratios between 4.7 and 11.4 (w/w), expressed as weight percent of solvent with respect to drug.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone compositions of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 2. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 25. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As shown in the cited figure, the injection of an amount of formulation corresponding to 15 mg risperidone to New Zealand White rabbits resulted in initial plasma levels 4h post-administration, which plasma levels were sustained up to 28 days in all solvent/risperidone ratios, although the lower the solvent/risperidone ratio, the more constant levels were achieved. All ratios studied showed an adequate control of the initial plasma levels during first 24h, however, the ratio 11.4 is not considered adequate because it exhibits a later uncontrolled drug diffusion/release during the following days

(days 2nd to 5th). Therefore it is consider that an appropriate solvent/risperidone ratio should be lower than 10 and until at least the lowest value tested (4).

Example 13: Study of the addition of a pH modifier.

The same risperidone implantable formulations were prepared by completely dissolving the polymer in the solvent (DMSO) and subsequently dispersing the drug in the mentioned polymeric solution with the optional addition of an alkaline agent such magnesium hydroxide.

Ingredient	Amount (mg)	
	No Alkaline agent	Alkaline agent
Resomer®RG503 (polymer)	100	100
Risperidone	25	25
Dimethyl sulfoxide (solvent)	233.3	233.3
Magnesium Hydroxide	--	8.3

RG503, 50:50 lactic/glycolic acid polymer (Boehringer Ingelheim)

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone compositions of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 2. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 26. The results are expressed as the addition of the risperidone plus 9-OH-

risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As shown in the cited figure, the injection of an amount of formulation corresponding to 15 mg risperidone to New Zealand White rabbits resulted in initial plasma levels since 4h post-administration up to at least 23 days. However, by the use of an alkaline agent within the polymer matrix, a more sustained plasma levels starting from 4h post-administration and an enlargement of the time showing therapeutic risperidone plasma levels up to at least 32 days is achieved.

Example 14: Study of reconstitution of the formulations.

Risperidone implantable formulations were prepared with the following composition:

Ingredient	Amount (mg)
Resomer®RG503 (polymer)	50
Risperidone	25
Dimethyl sulfoxide (solvent)	166.7

RG503, 50:50 lactic/glycolic acid polymer (Boehringer Ingelheim)

The risperidone selected for the compositions of this example showed a usual particle size distribution between 25-225 microns (not more than 10% of drug particles with a particle size smaller than 25 microns, and not more than 10% larger than 225 microns). Three different methods were applied to reconstitute the composition:

A) Vial. The polymeric solution was prepared by weighing the appropriate amounts of polymer and solvent and mixing them by vortexing until the polymer had completely dissolved in the solvent. Then, the appropriate risperidone amount was added to the polymeric solution and a homogeneous suspension was obtained by vortexing.

B) Syringes. The risperidone, the polymer and the solvent were weighed independently in syringes. The polymeric solution was then prepared by connecting the respective syringes by a fluid connector so that the solvent was moved from the syringe containing it to the syringe containing the polymer and then making several forward-backward cycles from one syringe to the other by pushing the respective plungers. Once

the polymer is completely dissolved in the solvent, the third syringe containing the risperidone was connected and a homogeneous suspension was then obtained by doing several additional cycles.

C) Freeze-drying. Polymer and risperidone were freeze-dried in a prefilled syringe and the solvent was placed in a second syringe. The syringes were connected by a fluid connector and then the solvent was moved to the syringe containing the freeze-dried polymer-risperidone mixture and finally several forward-backward cycles were repeated until a homogeneous suspension was achieved.

Preparation methods B and C can also be carried out by direct connection of syringes using female-male luer syringes.

In vitro release profile:

The risperidone release from formulations corresponding to the three different methods was evaluated according to the following procedure: the amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks by using a 21G needle followed by the careful addition of a pre-warmed release medium. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time (2h, 1d, 3d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d and 35d), 5 ml of release medium was collected and replaced with fresh buffer, and the amount of risperidone amount present in the sample was determined by UV spectrophotometry.

The profile of risperidone released from the implants is shown in Figure 27. The results are expressed as %Risperidone released from the formulation as a function of time. As it can be observed in Figure 27, the release profile of the implantable formulations prepared by the three different methods was the same during first 2 weeks. However, after 14 days the preparation method A (vial) resulted in a slightly slower release rate, probably due the higher porosity of the implants formed by the other 2 methods because of the air introduced to the formulation during the reconstitution process.

In vivo plasma levels after intramuscular administration to New Zealand rabbit

The risperidone compositions of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits was 2. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 28. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be seen in the cited Figure, the injection of an amount of formulation corresponding to 15 mg risperidone to New Zealand White rabbits resulted in initial plasma levels starting from 4h post-administration up to at least 28 days. The methods consisting on reconstitution of a formulation pre-filled in different containers by their mixing (Methods B and C) evoked slightly higher initial plasma levels. This could be due to the higher porosity, and consequently higher initial diffusion, of the implantable formulations prepared by these two methods in comparison with Method A (preparation inside a vial). This fact could be also the reason for their higher plasma levels during the first week after administration.

In vivo plasma levels after intramuscular administration to Beagle dog

The risperidone formulations of this example were also intramuscularly injected to Beagle dogs weighing an average of 10 kg. The amount injected corresponded to a dose of 25 mg risperidone and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of dogs was 3. After injection,

plasma levels were obtained at 0, 4h, 1d, 2d, 3d, 5d, 7d, 10d, 14d, 17d, 21d, 24d, 28d, 31d, 35d, 38d and 42d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 29. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be seen in the cited Figure, the injection of an amount of formulation corresponding to 25 mg risperidone to Beagle dogs resulted in well-controlled initial plasma levels with sustained levels up to at least 35 days using different preparation methods such as prior elaboration of polymeric solution followed by drug addition (vial, method A) or by direct reconstitution starting from solid components (syringes, method B).

Example 15: Study of the effect of sterilization by irradiation process.

In the present example, the composition of the risperidone implantable formulations was as follows maintaining always the same amounts of drug, polymer and solvent::

Composition	Irradiation (KGy)	Polymer lactic/ glycolic ratio	Polymer End Terminal group	Mean Molecular weight (g/mol)	Polymer Solution Viscosity (Pa.s)	Solvent
A	0	50:50	capped	27,020	1.62	DMSO
B	10	50:50	capped	23,189	1.30	DMSO
C	15	50:50	capped	22,182	1.00	DMSO
D	25	50:50	capped	20,991	0.81	DMSO
E	0	50:50	capped	39,708	5.97	DMSO
F	25	50:50	capped	27,891	1.78	DMSO

The implantable formulations were prepared by direct reconstitution of 2 prefilled syringes, first one with polymer and risperidone mixture, and second one with the solvent. Syringes were connected.

Syringes containing polymer plus risperidone mixtures were sterilized by β-irradiation in the range 10-25 KGy. As indicated in the table, two different polymer were tested, one is an end capped 50:50 polymer with mean Mw 27,020 g/mol, non irradiated or irradiated at 10, 15 or 25 KGy, and the other an end capped 50:50 polymer with mean Mw 39,708 g/mol, non irradiated or irradiated at 25 KGy.

Formulations A and E received sterilization irradiations that gave rise to different compositions due to different polymer molecular weight losses during the process; however, the inherent viscosity did not result below 0.25 dL/g in any case, and the viscosity of the polymer solution is maintained between the range 0.5-7 Pa.s previously studied as being adequate for this kind of long lasting implantable formulations (Example 9).

In vitro release profile:

The risperidone release from compositions of this example was evaluated according to the following procedure. The amount of formulation corresponding to 25 mg of risperidone was injected from prefilled syringes into flasks having a pre-warmed release medium by using a 21G needle. The release medium was 250 ml phosphate buffer pH= 7.4. The flasks were then placed into an oven at 37°C and kept under horizontal shaking at 50 rpm. At previously scheduled time points (2h, 1d, and periodically up to 28 days) 5 ml of release medium was collected and replaced with fresh buffer and the amount of risperidone present in the sample was determined by UV spectrophotometry. The profile of risperidone released from the implants of this example is shown in Figure 30 and Figure 31. The results are expressed as % drug released from implants as a function of time.

As it can be observed in the Figure 30, the release of risperidone from the same formulation either non irradiated (composition A) or irradiated at different levels

(compositions B, C and D) in the range 10-25 KGy resulted in very similar profiles because polymer solution viscosities were still within the preferred established range 0.7 to 2.0 Pa.s. Figure 31 shows how the other polymer with a higher Mw (39,708 g/mol) (composition E) which presents an slighlty slower release profile, once it is irradiated (composition F) presents a release profile closer to the non-irradiated lower Mw polymer (composition A), due to the loss of molecular weight during sterilization process, which leads to a composition with polymer solution viscosity key parameter within preferred ranges 0.7-2.0 Pa.s.

In vivo plasma levels after intramuscular administration to New Zealand rabbit:
The risperidone compositions A, B, C, D and G of this example were intramuscularly injected to New Zealand White rabbits weighing an average of 3 kg. The amount injected corresponded to a dose of 15 mg risperidone, and the composition was intramuscularly placed in the left hind leg using a syringe with a 20G needle. Total number of rabbits per composition was 3. After injection, plasma levels were obtained at 0, 4h, 1d, 2d, 5d, 7d, 10d and periodically up to 28 days.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 32 and Figure 33. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be observed in these Figures, the injection of an amount of composition equivalent to 15 mg risperidone to New Zealand White rabbits resulted in very similar plasma levels as could be predicted since *in vitro* behaviour was very similar after irradiation. Figure 32 revealed not extraordinary changes in the risperidone active moiety plasma levels when a formulation comprising a 27,020 g/mol mean molecular weight polymer (composition A), was irradiated at 10, 15 or 25 KGy (composition B, C and D, respectively) since key parameter such as polymer solution viscosity is still inside the previously preferable determined range of 0.7 to 2.0 Pa.s.

A higher molecular weight polymer (39,708 g/mol), with polymer solution viscosity out of the preferable range (5.97 Pa.s, composition E), upon irradiation at 25 KGy (since higher molecular weight polymers suffer proportionally higher molecular weight losses during irradiation) leads to a polymer with lower inherent viscosity and consequently lower but still adequate polymer solution viscosity of 1.78 Pa.s (composition F). That higher molecular weight polymer, after 25 KGy irradiation, resulted extremely close to the lower one without any irradiation (compostion A) in both molecular weight and polymer solution viscosity, therefore fulfilling in this manner the polymer solution viscosity parameter leading to adequate long lasting implantable systems in line with the present invention, and experimenting a very similar *in vivo* behaviour (plasma levels profile) as shows Figure 33.

Comparative Example 2 (not according to the invention)

Risperidone implantable formulations were prepared according to procedures described in US 5,688,801.

In vivo plasma levels after intramuscular administration to Beagle dog

The risperidone formulations of this example were intramuscularly injected to Beagle dogs weighing an average of 10 kg after resuspension of microparticles in 2 ml of a 2.5% (in weight) carboxymethyl cellulose solution in water. The amount injected corresponded to a dose of 25 mg risperidone and the composition was intramuscularly placed in the left hind leg. Total number of dogs was 6. After injection, plasma levels were obtained at 0, 1d, 2d, 6d, 9d, 13d, 15d, 17d, 19d, 21d, 23d, 26d, 29d, 33d, 35d, 42d and 56d.

The kinetics of the plasma levels corresponding to the risperidone active moiety was evaluated by measuring both risperidone and its active metabolite 9-OH-risperidone in the plasma samples. The profile of the risperidone active moiety plasma levels is shown in Figure 34. The results are expressed as the addition of the risperidone plus 9-OH-risperidone concentrations (ng/ml) as a function of time, since the therapeutic activity of 9-OH-risperidone is substantially equivalent to that of risperidone. As it can be seen in

the cited Figure, the results of this test showed that the administration of risperidone in preformed microparticles, according to procedures described in the prior art, fails to provide significant plasma levels of risperidone active moiety in dogs until the third week following administration. The plasma levels observed among the 6 animals also showed a poor reproducibility, and the rise was typically observed from approximately day 21st until approximately day 28th following administration, to then diminish at a similar rate, thereby providing a peak of plasma level with an approximate extension of 2 weeks. These profiles are completely different to the profiles observed in the examples according to the invention and clearly demonstrates the difference between the plasma levels obtained with the composition according to the invention compared to those obtained according to the prior art.

From the above experiments it can be concluded that the viscosity of the polymeric solution (polymer + solvent), surprisingly shows a stronger influence on the control of the drug release than other various factors that could conceivably be considered as having a stronger effect, such as the nature of the polymer or its concentration. This result is unexpected and surprising in the light of the prior art.

It can also be concluded that, when a certain portion of the polymer is removed at a constant risperidone amount, –or, in other words, that the drug/polymer mass ratio is increased-, the initial release is lower and consequently the plasma level profiles are flattened. This effect is likewise surprising, since the presence of a lower amount of polymer could be *a priori* related to a lower capacity to retain the drug and providing a worse initial release control.

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 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.

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 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.

7. The composition according to claim 6, wherein the mass ratio between the weight of the solution comprising the polymer and the solvent and the drug is between 12 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 7 and 6.5.

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 about 6.66.

10. The composition according to any of the previous claims further comprising $Mg(OH)_2$ in a molar ratio between 2/3 and 2/5, expressed as the molar ratio of drug to $Mg(OH)_2$.

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

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

13. A pharmaceutical kit suitable for the in situ formation of a biodegradable implant in a body comprising the composition of any one of claims 1-12, wherein the drug and the biocompatible polymer are contained in a first container, and the solvent is contained in a second, separate container.

14. The pharmaceutical kit according to claim 13, wherein at least one of the first and second containers is a syringe, a vial, a device or a cartridge, either disposable or not.

15. The pharmaceutical kit according to claim 14, wherein both the first and the second containers are disposable syringes.

16. The pharmaceutical kit according to claim 15, wherein the syringes are connectable through a connector device or a direct thread.