Sustained Release Formulations Using Non-Aqueous Carriers

Related Applications

This application claims priority to US Application No. 61/094,381 filed September 4, 2008, the disclosure of which is incorporated by reference herein.

Background

Injectable sustained release formulations offer the opportunity to provide therapeutic amounts of active pharmaceutical ingredients over an extended period of time from a single injection, thus eliminating the need for once or twice daily injections. Presently available injectable sustained release formulations utilizing, for example, microspheres and an aqueous carrier, carry several disadvantages. The formulations do not offer long term stability in the aqueous carrier, thus necessitating separate packaging and storage for the microspheres and aqueous carrier, and the patient must take several steps to combine the microspheres and aqueous carrier before administering the injection.

Another disadvantage of presently available injectable microsphere formulations is a large burst release following injection, which causes an undesirable in vivo release of active pharmaceutical ingredient in a single burst. When medications have toxic or deleterious side effects, this is undesirable.

There is a need for formulations and methods of safely administering sustained release pharmaceutical formulations to patients so that the active ingredient will be released in vivo over an extended period of time and without an unacceptable initial burst release. Ideally the active ingredient is released so as to maintain levels within the therapeutic window, i.e., in the concentration range above that needed to cause the desired clinical effect, but below that where undesirable side effects outweigh the benefits of the drug. It is also necessary that this active pharmaceutical ingredient be provided in a manner that is easy and convenient for the patient to self-administer and that is provided in a formulation that maintains stability for a long period of time in a liquid state. The disclosure is directed to these as well as other important ends.

Summary

The disclosure provides formulations comprising microspheres that contain active pharmaceutical ingredients, where the microspheres are suspended in a non-aqueous pharmaceutically acceptable carrier. The formulations are one-component injectable microsphere formulations, such that they do not require the patient to mix the formulation with a

pharmaceutically acceptable carrier prior to injection. The disclosure offers distinct advantages over prior two-component formulations by providing for a long shelf life of the composition in the carrier, sustained release of the active pharmaceutical ingredient, a less complex carrier, a more easily manufactured carrier, a less complex injection-delivery apparatus, a kit with less components, and ease of use by patients.

The disclosure provides sustained release formulations comprising a pharmaceutically acceptable carrier which consists essentially of one or more triglycerides which comprise C_6-C_{12} fatty acids; and microspheres which consist essentially of a poly(lactide-co-glycolide) polymer having dispersed therein about 1% to 10% (w/w) exenatide and about 0.1% to 5% (w/w) of a sugar; wherein the ratio of lactide:glycolide in the polymer is about 70:30 to 30:70, or about 1:1. In one aspect, the present disclosure refers to a manufactured pre-mixed formulation for injection comprising a suspension of: (i) a pharmaceutically acceptable non-aqueous carrier which comprises one or more triglycerides of C_6-C_{12} fatty acids; and (ii) microspheres which comprise a biocompatible, biodegradable polymer which is a poly(lactide-co-glycolide) polymer and an active pharmaceutical ingredient that is exenatide. In another aspect, the present disclosure refers to a use of the formulation as disclosed herein in the manufacture of a medicament for treating diabetes; stimulating insulin release; lowering plasma glucagon; reducing food intake; reducing appetite; decreasing gastric motility; delaying gastric emptying; lowering plasma lipid levels; treating impaired glucose tolerance; treating hyperglycemia; treating obesity; treating overweight; treating fatty liver disease; or treating non-alcoholic steatohepatitis in a patient in need thereof wherein said formulation is to be administered to the patient in need thereof. In another aspect, the present disclosure refers to the formulation as disclosed herein for use in therapy. In another aspect, the present disclosure refers to a kit comprising a container which comprises the formulation as disclosed herein and instructions for use. In yet another aspect, the present disclosure refers to a manufactured pre-mixed formulation as disclosed herein for injection consisting essentially of a suspension of: (i) a pharmaceutically acceptable carrier which comprises one or more triglycerides of C_6-C_{12} fatty acids; and (ii) microspheres which consist essentially of a poly(lactide-co-glycolide) polymer having dispersed therein about 5% (w/w) exenatide as active pharmaceutical ingredient and about 2% (w/w) sucrose; wherein the ratio of lactide:glycolide in the polymer is about 1:1.

In one example, the exenatide is present in an amount of 1% to 5% (w/w) or 5% (w/w) and the sugar is present in an amount of 2% (w/w). The sugar may be, e.g., glucose, dextrose, galactose, maltose, fructose, mannose, sucrose, lactose, trehalose, raffinose, acarbose, glycol, glycerol, erythritol, threitol, arabitol, ribitol, sorbitol, dulcitol, iditol, isomalt, maltitol, lactitol, mannitol, xylitol, or a combination of two or more thereof. In one example, the sugar is sucrose. The formulation is a suspension whereby the microspheres are suspended in the carrier. In one example, the total pore volume of the microspheres is about 0.1 mL/g or less, as determined using mercury intrusion porosimetry, to provide a release profile having a ratio of maximum serum concentration of exenatide during the period of release (C_{max}) to average serum concentration of exenatide during the period of release (C_{ave}) of about 3 or less. Further, although the microspheres are formulated in oil (i.e. a carrier as disclosed herein), the microspheres do not necessarily have oil contained within the interior spaces or pores, or within a substantial number of interior spaces or pores, of the microspheres, and yet can achieve the surprising properties disclosed herein.

The disclosure provides sustained release formulations comprising a pharmaceutically acceptable non-aqueous carrier and microspheres which comprise a biocompatible,

biodegradable polymer and an active pharmaceutical ingredient. In one example, the total pore volume of the microspheres is about 0.1 mL/g or less, as determined using mercury intrusion porosimetry, to provide a release profile having a ratio of maximum serum concentration of the active pharmaceutical ingredient during the period of release (C_{max}) to average serum concentration of the active pharmaceutical ingredient during the period of release (C_{ave}) of about 3 or less. Further, although the microspheres are formulated in oil (i.e. a carrier as disclosed herein), in some examples the microspheres do not have oil contained within the interior spaces or pores, or do not have oil within a substantial number of interior spaces or pores of the microspheres, and yet can achieve the surprising properties disclosed herein. The formulation is a suspension whereby the microspheres are suspended in the carrier. The non-aqueous carrier may be an oil, such as fractionated oils, triglycerides, diglycerides, monoglycerides, propylene glycol fatty acid diesters, and the like.

In one example the active ingredient is not soluble in the carrier. In various other examples the active ingredient has a solubility in the carrier of less than 0.01 mg/ml, or less than 0.05 mg/ml or less than 0.1 mg/ml or less than 0.5 mg/ml or less than 1 mg/ml. In still other examples the active pharmaceutical ingredient has a solubility in the carrier such that less than 10% of the active ingredient in the formulation is contained within the carrier with the remaining 90% contained within the microparticles. In further examples less than 5% or less than 2% or less than 1% or less than 0.5% of the active ingredient is contained in the carrier. In still further examples where it is desirable to have some active ingredient immediately available, it may also be directly incorporated into the carrier in a pharmaceutically effective amount.

The disclosure provides a kit, available to a patient or medical service provider. The kit contains a container having a formulation of the disclosure, and instructions for use. In one example the container is a pen injector. The pen injector can be a single-dose pen injector or a multi-dose pen injector. In one example the container is a vial, which can be either a single-dose vial or a multi-dose vial. In another example the container is a cartridge, such as a cartridge for use in a injection apparatus. The cartridge can be either a single-dose or a multi-dose cartridge. In different examples the kit contains 1, 2, 3, 4, or even 5 or more such containers carrying a formulation of the disclosure. One further advantage of the formulations is that in one example the container is provided preservative free. But in other examples a preservative can be soluble in the selected carrier and provided in the formulation.

Claims

What is claimed is:

1. A manufactured pre-mixed formulation for injection comprising a suspension of:

(i) a pharmaceutically acceptable non-aqueous carrier which comprises one or more triglycerides of C_6-C_{12} fatty acids; and

(ii) microspheres which comprise a biocompatible, biodegradable polymer which is a poly(lactide-co-glycolide) polymer and an active pharmaceutical ingredient that is exenatide.

2. The formulation of claim 1, wherein the microspheres have dispersed therein 1% to 10% (w/w) exenatide and 0.1% to 5% (w/w) sugar; particularly,

wherein the sugar is glucose, dextrose, galactose, maltose, fructose, mannose, sucrose, lactose, trehalose, raffinose, acarbose, glycol, glycerol, erythritol, threitol, arabitol, ribitol, sorbitol, dulcitol, iditol, isomalt, maltitol, lactitol, mannitol, xylitol, or a combination of two or more thereof.

3. The formulation of claim 1 or claim 2, wherein the pharmaceutically acceptable non-aqueous carrier is a fractionated or unfractionated coconut oil, a fractionated or unfractionated palm oil, a fractionated or unfractionated palm kernel oil, a fractionated or unfractionated sesame oil, a fractionated or unfractionated soybean oil, a fractionated or unfractionated almond oil, a fractionated or unfractionated rapeseed oil, a fractionated or unfractionated corn oil, a fractionated or unfractionated sunflower oil, a fractionated or unfractionated peanut oil, a fractionated or unfractionated olive oil, a fractionated or unfractionated castor oil, a fractionated or unfractionated soybean oil, a fractionated or unfractionated safflower oil, a fractionated or unfractionated cottonseed oil, ethyl oleate, or a combination of two or more thereof.

4. The formulation of any one of claims 1 to 3, wherein the pharmaceutically acceptable non-aqueous carrier further comprises one or more monoglycerides, one or more diglycerides, one or more triglycerides, or a combination of two or more thereof.

5. The formulation of any one of claims 1 to 3, wherein the pharmaceutically acceptable non-aqueous carrier comprises (i) a triglyceride which comprises an ester of a C_6 fatty acid; (ii) a triglyceride which comprises an ester of a C_8 fatty acid; (iii) a triglyceride which comprises an ester of a C_{10} fatty acid; (iv) a triglyceride which comprises an ester of a C_{12} fatty acid; (v) a triglyceride which comprises esters of three C_8 fatty acids; (vi) a triglyceride which comprises esters of three C_{10} fatty acids; (vii) a triglyceride which comprises esters of two C_8 fatty acids and one C_{10} fatty acid; (viii) a triglyceride which comprises esters of two C_{10} fatty acids and one C_8 fatty acid; (ix) a triglyceride which comprises esters of two C_8 fatty acids and one C_6 fatty acid; (x) a triglyceride which comprises esters of two C_{10} fatty acids and one C_6 fatty acid; (xi) a triglyceride which comprises esters of one C_8 fatty acid, one C_{10} fatty acid, and one C_{12} fatty acid; (xii) a triglyceride which comprises esters of one C_8 fatty acid, one C_{10} fatty acid, and one C_6 fatty acid or (xiii) a combination of two or more thereof.

6. The formulation of any one of claims 1 to 3, wherein the pharmaceutically acceptable non-aqueous carrier comprises a triglyceride which comprises esters of (i) 0 to 2 wt% C_6 fatty acid, 65 to 80 wt% C_8 fatty acid, 20 to 35 wt% C_{10} fatty acid, and 0 to 2 wt% C_{12} fatty acid; (ii) 0 to 2 wt% C_6 fatty acid, 50 to 65 wt% C_8 fatty acid, 30 to 45 wt% C_{10} fatty acid, and 0 to 2 wt% C_{12} fatty acid; (iii) 0 to 2 wt% C_6 fatty acid, 45 to 65 wt% C_8 fatty acid, 30 to 45 wt% C_{10} fatty acid, 0 to 3 wt% C_{12} fatty acid; and 0 to 5 wt% linoleic acid; or (iv) 0 to 2 wt% C_6 fatty acid, 45 to 55 wt% C_8 fatty acid, 30 to 40 wt% C_{10} fatty acid, 0 to 3 wt% C_{12} fatty acid, and 10 to 20 wt% succinic acid.

7. The formulation of claim 6, wherein the pharmaceutically acceptable non-aqueous carrier comprises 0 to 2 wt% C_6 fatty acid, 50 to 65 wt% C_8 fatty acid, 30 to 45 wt% C_{10} fatty acid, and 0 to 2 wt% C_{12} fatty acid.

8. The formulation of any one of claims 3 to 6, wherein the triglycerides comprise up to 2% C_{14} fatty acids.

9. The formulation of claim 1, further comprising a pharmaceutically acceptable excipient; particularly, wherein the pharmaceutically acceptable excipient is a sugar, a sugar alcohol, an antioxidant, a preservative, or a combination of two or more thereof; and/or, wherein the pharmaceutically acceptable excipient is sucrose, glucose, dextrose, galactose, maltose, trehalose, fructose, maltodextrin, glycol, glycerol, erythritol, threitol, arabitol, ribitol, sorbitol, dulcitol, iditol, isomalt, maltitol, lactitol, mannitol, xylitol, benzoic acid, sorbic acid, meta cresol, sodium benzoate, potassium sorbate, methylparaben, propylparaben, butylparaben, benzalkonium chloride, sodium metabisulfite, butylated hydroxy anisole, butylated hydroxy toluene, sodium sulfite, tocopherol, thymol, ascorbate, propyl gallate, or a combination of two or more thereof.

10. The formulation of claim 1, wherein the formulation does not further comprise a gel-forming agent.

11. Use of the formulation of any one of claims 1 to 10 in the manufacture of a medicament for treating diabetes; stimulating insulin release; lowering plasma glucagon; reducing food intake; reducing appetite; decreasing gastric motility; delaying gastric emptying; lowering plasma lipid levels; treating impaired glucose tolerance; treating hyperglycemia; treating obesity; treating overweight; treating fatty liver disease; or treating non-alcoholic steatohepatitis in a patient in need thereof wherein said formulation is to be administered to the patient in need thereof.

12. The formulation of any one of claims 1 to 10 for use in therapy.

13. A kit comprising a container which comprises the formulation of any one of claims 1 to 10 and instructions for use.

14. The kit of claim 13, wherein the container is a single-dose or multi-dose pen injector, single-dose or multi-dose vial, or single-dose or multi-dose cartridge.

15. A manufactured pre-mixed formulation according to claim 1 for injection

consisting essentially of a suspension of: (i) a pharmaceutically acceptable carrier which comprises one or more triglycerides of C_6-C_{12} fatty acids; and (ii) microspheres which consist essentially of a poly(lactide-co-glycolide) polymer having dispersed therein about 5% (w/w) exenatide as active pharmaceutical ingredient and about 2% (w/w) sucrose;

wherein the ratio of lactide:glycolide in the polymer is about 1:1.