Novel Dutogliptin formulations and their preparation

Background

Dutogliptin (CAS 852329-66-9) is designed as a regenerative medicine to reduce and repair heart muscle injury. It acts as an inhibitor of dipeptidylpeptidase-IV (DPP4) enzyme, which is involved in the degradation of stromal-derived factor-1α (SDF-1α). The drug is given to patients in actual clinical trials as twice-a-day, subcutaneous injection of 60 to 100 mg combined with a subcutaneous dose of filgrastim.

Usually, Dutogliptin is prepared as its tartrate salt. Dutogliptin was originally administered orally. But for acute cardiac indications it needs to be administered parenterally to achieve optimal pharmacokinetic and pharmacodynamic activity. To achieve the required activity with the current formulation it needs to be administered at least twice a day for 2 weeks, resulting patient compliance, acceptance, and injection site issues. Therefore it is desired to reduce the frequency of parenteral administration. It is thus an aim of the present application to deal with such a desire and reducing the number of parenteral administrations, The objective of this invention is thus the provision of preparations of (freeze dried) multilamellar vesicles (MLV) containing encapsulated Dutogliptin and provide liposomal Dutogliptin formulations. These are advantageously suitable for, e.g. subcutaneous (s.c.) or intramuscular (i.m.) application.

Brief Summary

The present disclosure provides a first item which refers to a method for the preparation of a liposomal Dutogliptin formulation, comprising the steps:

(A)

A.1) providing an organic phase, wherein the organic phase comprises

(a) one or more phospholipids, wherein the amount of said one or more phospholipids is between 3%(w/w) and 30%(w/w) based on the sum of (a), (b) and (c), preferably 22.36%(w/w) based on the sum of (a), (b), and (c);

C.3) mixing the aqueous phase and the organic phase until a ratio between 3:1 and 1:3, preferably of 1:1, aqueous phase to organic phase is reached resulting in in a nano-disperse system comprising Dutogliptin;

C.4) lyophilize the in a nano-disperse system comprising Dutogliptin resulting in a lyophilizate;

C.5) reconstitute the lyophilizate of step C.4 with an aqueous solution resulting in a liposomal Dutogliptin formulation, wherein the aqueous solution comprises between 80%(w/w) and 100%(w/w) of an aqueous medium based on the total weight of the aqueous solution, optionally further comprising a tonicity adjusting agent, wherein the amount of the tonicity adjusting agent is at most 20%(w/w) based on the total weight of the aqueous solution, optionally further comprising a buffer system, preferably, wherein the final concentration of Dutogliptin in the liposomal Dutogliptin formulation is between 25 mg/ml and 60 mg/ml.

One aspect of the present disclosure refers to a method for the preparation of a liposomal Dutogliptin formulation, comprising the steps:

(B)

B.1) providing an organic phase comprising

(a) one or more phospholipids, wherein the amount of said one or more phospholipids is between 3%(w/w) and 30%(w/w) based on the sum of (a), (b) and (c), preferably 22.36%(w/w) based on the sum of (a), (b) and (c);

(b) one or more organic solvents selected from the group consisting of anisole, ethylacetate, 1,4-dioxane, dimethylcarbonate, dimethylsulfoxide, glycofurol, N,N-dimethylacetamide, N,N-dimethylformamide, N-methyl-2-pyrrolidone (NMP), isopropylideneglycerol, 1-butanol, 2-butanol and tert-butanol or a combination of any of the foregoing; wherein the amount of the said one or more organic solvents is between 60%(w/w) and 97%(w/w) based on the sum of (a), (b) and (c), preferably 74.43%(w/w) based on the sum of (a), (b) and (c);

(c) optionally one or more further organic component(s), which are neither (a) nor (b), wherein the amount of said one or more further organic component(s) is at most 10% based on the sum of (a), (b) and (c);

wherein the sum of (a), (b) and (c) sums up to 100%; and

B.2) providing an aqueous phase comprising

(d) an aqueous medium, wherein the amount of the aqueous medium is between 66%(w/w) and 90%(w/w) based on the sum of (d), (e) and (f), preferably 84%(w/w) based on the sum of (d), (e) and (f);

(e) optionally one or more further components selected from the group consisting of a buffer system, NaOH, and HCl, wherein the amount of all further components is at most 2%(w/w) based on the sum of (d), (e) and (f);

(f) optionally a bulking agent, preferably trehalose, wherein the amount of the bulking agent is at most 10%(w/w) based on the sum of (d), (e) and (f), preferably between 3%(w/w) and 7%(w/w) based on the sum of (d), (e) and (f);

wherein the sum of (d), (e) and (f) sums up to 100%; and

B.3) mixing the aqueous phase and the organic phase until a ratio between 3:1 and 1:3, preferably of 1:1, aqueous phase to organic phase is reached resulting in a nano-dispersed system;

B.4) lyophilize the nano-disperse system resulting in a lyophilizate;

B.5) reconstitute the lyophilizate of step B.4 with an aqueous solution resulting in a liposomal Dutogliptin formulation, preferably wherein the final concentration of Dutogliptin in the liposomal Dutogliptin formulation is between 25 mg/ml and 60 mg/ml, wherein the aqueous solution comprises

(i) 67%(w/w) and 100%(w/w) of an aqueous medium based on the total weight of the aqueous solution, optionally further comprising a tonicity adjusting agent, wherein the amount of the tonicity adjusting agent is at most 20%(w/w) based on the total weight of the aqueous solution optionally further comprising a buffer system,

(ii) Dutogliptin, preferably in form of its tartrate salt or in form of its free base form, wherein the amount of Dutogliptin is between 5%(w/w) and 13%(w/w), more preferably 10±0.5)%(w/w) based on the total weight of the aqueous solution when the Dutogliptin is present in its tartrate salt form or free base form; or (6±0.4)%(w/w) based on the total weight of the aqueous solution when the Dutogliptin is present in its free base form.

One example of the disclosure refers to the method, wherein the organic solvent is tert-butanol (TBA).

Another example of the disclosure refers to the method, wherein the organic phase further comprises cholesterol

and wherein the amount of cholesterol is between 2.5%(w/w) and 4%(w/w), preferably 3.2%(w/w).

Another example of the disclosure refers to the method, wherein the organic phase comprises as a phospholipid lecithin and wherein the amount of lecithin is between 18.1%(w/w) and 26.2%(w/w) more preferably 22.13%(w/w).

Another example of the disclosure refers to the method, wherein the organic phase further comprises as phospholipid(s) PG, preferably DOPG-Na, wherein the total amount of PG is between 0,1%(w/w) and 0.4%(w/w), preferably 0.23%(w/w).

Another example of the disclosure refers to the method, wherein the pH of the aqueous phase is between 7 and 7.8, preferably 7.4.

Another example of the disclosure refers to the method, wherein the D90 of the liposomes of the liposomal Dutogliptin formulation resulting from the reconstitution step is between 1 µm and 4.5 µm.

Another example of the disclosure refers to the method, wherein the only solvent of an aqueous solution is water.

Another example of the disclosure refers to the method, wherein the aqueous solution is an aqueous NaCl solution wherein the amount of NaCl is between 8g/l and 10 g/l, preferably between 8.8 g/l and 9.2 g/l, more preferably 9 g/l.

Another example of the disclosure refers to the method, wherein the aqueous solution in Step B.5 is a Dutogliptin tartrate solution.

Another example of the disclosure refers to the latter example, wherein the aqueous solution further comprises 9 g/l NaCl.

Another example of the disclosure refers to the method, wherein the total amount of Dutogliptin in the liposomal Dutogliptin formulation is between 60 mg and 100 mg.

Another aspect refers to a liposomal Dutogliptin formulation preparable according to the method of the disclosure, wherein the concentration of Dutogliptin in the liposomal Dutogliptin formulation is between 25 mg/ml and 60 mg/ml.

Another aspect refers to a liposomal Dutogliptin formulation comprising

(i) an aqueous medium, preferably water, wherein the amount of the aqueous medium is between 65%(w/w) and 90%(w/w) based on the total weight of the liposomal Dutogliptin formulation;

(ii) optionally a lipid, preferably cholesterol, wherein the amount of said lipid, preferably cholesterol is between 1%(w/w) and 2.5%(w/w) based on the total weight of the liposomal Dutogliptin formulation;

(iii) one or more phospholipid(s), wherein the amount of said one or more phospholipid(s) is between 7%(w/w) and 15%(w/w), preferably (11.2±0.4)(w/w), based on the total weight of the liposomal Dutogliptin formulation, preferably, wherein the one or more phospholipids are phosphatidylcholine (PC), phosphatidylglycerol (PG) and 1,2-distearoyl-*sn*-glycero-3-[phospho(1′-*rac*-glycerol)] (DSPG);

(iv) optionally one or more agent(s) selected from the group consisting of glycine, arginine, proline, or any other amino acid known to be suitable as a bulking agent, a saccharide component selected from the group consisting of sucrose, trehalose, arabinose, erythritol, fructose, galactose, glucose, lactose, maltitol, maltose, maltotriose, mannitol, mannobiose, mannose, ribose, sorbitol, xylitol,

xylose, dextran, dextrose, and NaCl, wherein the total amount of said one or more agent(s) is between 1.5%(w/w) and 5.5%(w/w);

(v) Dutogliptin, wherein the amount of Dutogliptin, preferably in its tartrate salt form or free base form, is between 3%(w/w) and 12%(w/w), preferably (5.3±0.3) (w/w) based on the total weight of the liposomal Dutogliptin formulation and the

final concentration of Dutogliptin in the liposomal Dutogliptin formulation is between 25 mg/ml and 60 mg/ml;

wherein the sum of (i) to (v) sums up to 100%).

Another aspect refers to a kit comprising a lyophilizate of the disclosure in a container and a pharmaceutical aqueous solution of the disclosure in a second container.

One example of the disclosure refers to the kit, further comprising a manual how to combine the content of the first and second container to receive a liposomal Dutogliptin formulation of the disclosure; or the liposomal Dutogliptin formulation of the disclosure.

Definitions

If not stated otherwise, amounts in % refer to % (weight/weight) ((w/w)).

If not explicitly mentioned otherwise (e.g. by using a term such as “a specific” meaning “one”), the term “a” is an indefinite article encompassing “one” and “one or more” / “more than one“ noun(s) following the term “a”.

The term “amount of one or more” components such as the amount of one or more organic solvent(s) refers to the total sum of all such components. For example, if two organic solvents are present in an organic phase, e.g. 20%(w/w) based on the total amount of the organic phase tert-butanol and 10%(w/w) based on the total weight of the organic phase propanol the amount of the said one or more organic solvents (the two organic solvents propanol and tert-butanol) is 30%(w/w) based on the total weight of the organic phase.

A “buffer” or “buffer system” as used herein is used to prevent major changes in the pH of a solution, and suitable examples are well-known to the skilled formulator.

A “bulking agent” as used herein and as the name implies, form the bulk of a lyophilized product, and provide an adequate structure to a lyophilized cake. Non limiting examples of bulk agents are mannitol, glycine, arginine, proline, glucose, sucrose, lactose, trehalose, and dextran.

The term “Cholesterol” refers to 3β-Hydroxy-5-cholestene (CAS No.: 57-88-5). Examples of derivatives of cholesterol are cholesteryl sulfate and its salts (e.g., sodium salt), cholesteryl hemisuccinate, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of