NOVEL FORMULATIONS

FIELD OF THE INVENTION

[0001] This invention relates inter alia to rapid acting aqueous liquid formulations of insulin and insulin analogues. Such formulations are suitable for the treatment of subjects suffering from diabetes mellitus, especially Type 1 diabetes mellitus.

BACKGROUND OF THE INVENTION

[0002] Diabetes mellitus ("diabetes") is a metabolic disorder associated with poor control of blood sugar levels leading to hypo or hyperglycemia. Untreated diabetes can lead to serious microvascular and macrovascular complications including coronary artery disease, peripheral artery disease, stroke, diabetic nephropathy, neuropathy and retinopathy. The two main types of diabetes are (i) Type 1 diabetes resulting from the pancreas not producing insulin for which the usual treatment is insulin replacement therapy and (ii) Type 2 diabetes where patients either produce insufficient insulin or have insulin resistance and for which treatments include insulin sensitising agents (such as metformin or pioglitazone), traditional insulin secretagogues (such as sulfonylureas), SGLT2 inhibitors (such as dapagliflozin, canagliflozin and empagliflozin) which reduce glucose absorption in the kidneys and so promote glucose excretion, GLP-1 agonists (such as exenatide and dulaglutide) which stimulate insulin release from pancreatic beta cells and DPPIV inhibitors (such as sitagliptin or vildagliptin) which inhibit breakdown of GLP-1 leading to increased insulin secretion. Patients with Type 2 diabetes may eventually require insulin replacement therapy.

[0003] For patients requiring insulin replacement therapy, a range of therapeutic options are possible. The use of recombinant human insulin has in recent times been overtaken by use of insulin analogues which have modified properties, for example, are longer acting or faster acting than normal insulin. Thus, a common regimen for a patient involves receiving a long acting basal insulin supplemented by a rapid acting insulin around mealtimes.

[0004] Insulin is a peptide hormone formed of two chains (A chain and B chain, respectively 21 and 30 amino acids in length) linked via disulfide bridges. Insulin normally exists at neutral pH in the form of a hexamer, each hexamer comprising three dimers bound together by zinc ions. Histidine residues on the insulin are known to be involved in the interaction with the zinc ions. Insulin is stored in the body in the hexameric form but the monomer form is the active form. Traditionally, therapeutic compositions of insulin have also been formulated in hexameric form in the presence of zinc ions. Typically, there are approximately three zinc cations per one insulin hexamer. It has been appreciated that the hexameric form is absorbed from the injection site considerably more slowly than the monomeric and dimeric form. Therefore, a faster onset of insulin action can be achieved if the hexameric form is destabilised allowing a more rapid dissociation of the zinc-bound hexamer into dimers and monomers in the subcutaneous space following injection. Three insulin analogues have been genetically engineered with this principle in mind. A first is insulin lispro (Humalog®) in which residues 28 and 29 of the B chain (Pro and Lys respectively) are reversed, a second is insulin aspart (NovoLog®) in which residue 28 of the B chain, normally Pro, is replaced by Asp and a third is insulin glulisine (Apidra®) in which residue 3 of the B chain, normally Asn, is replaced by Lys and residue 29 of the B chain, normally Lys, is replaced by Glu.

[0005] Whilst the existing rapid acting insulin analogues can achieve a more rapid onset of action, it has been appreciated that an even more rapid acting ("ultra rapid acting") insulins can be achieved by removing the zinc cations from insulin altogether. Unfortunately, the consequence of the hexamer dissociation is typically a considerable impairment in insulin stability both with respect to physical stability (e.g. stability to aggregation) and chemical stability (e.g. stability to deamidation). For example, monomeric insulin or insulin analogues having a rapid onset of action are known to aggregate and become physically unstable very rapidly because the formulation of insoluble aggregates proceeds via monomers of insulin. Various approaches to addressing this problem have been described in the art:

[0006] U.S. Pat. No. 5,866,538 (Norup) describes insulin preparations of superior chemical stability comprising human insulin or an analogue or derivative thereof, glycerol and/or mannitol and 5 to 100 mM of a halogenide (e.g. NaCl).

[0007] U.S. Pat. No. 7,205,276 (Boderke) addresses the stability problems associated with preparing zinc free formulations of insulin and insulin derivatives and analogues and describes an aqueous liquid formulation comprising at least one insulin derivative, at least one surfactant, optionally at least one preservative and optionally at least one of an isotonicizing agent, a buffer and an excipient, wherein the formulation is stable and free from or contains less than 0.4% (e.g. less than 0.2%) by weight of zinc based on the insulin content of the formulation. The preferred surfactant appears to be polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate).

[0008] US2008/0194461 (Maggio) describes formulations of peptides and polypeptides including insulin which contain an alkylglycoside, which component is said to reduce aggregation and immunogenicity.

[0009] WO2012/006283 (Pohl) describes formulations containing insulin together with a zinc chelator such as ethylenediaminetetraacetate (EDTA). Modulating the type and quantity of EDTA is said to change the insulin absorption profile. Calcium EDTA is the preferred form of EDTA since it is said to be associated with reduced pain at the injection site and is less likely to remove calcium from the body. Preferred formulations also contain citrate which is said to further enhance absorption and to improve the chemical stability of the formulation.

[0010] US2010/0227795 (Steiner) describes a composition comprising insulin, a dissociating agent such as citric acid or sodium citrate, and a zinc chelator such as EDTA wherein the formulation has a physiological pH and is a clear aqueous solution. The formulations are said to have improved stability and rapid onset of action.

[0011] WO2015/120457 (Wilson) describes stabilized ultra-rapid acting insulin formulations comprising insulin in combination with a zinc chelator such as EDTA, a dissolution/stabilization agent such as citric acid, a magnesium salt, a zinc compound and optionally additional excipients.

[0012] Further approaches to accelerating the absorption and effect of insulin through the use of specific accelerating additives have been described: