1.4. Oral insulin delivery

1.4.1. Insulin: physicochemical properties and function

Insulin was discovered in 1921 and shortly afterwards was described as a protein. Insulin is a polypeptide hormone, which is synthesized in pancreatic β -cells. Its synthesis involves sequential cleavage of its two precursor molecules preproinsulin and proinsulin (Joshi et al., 2007). Following synthesis, the preproinsulin molecule undergoes rapid enzymatic cleavage to proinsulin, which contains the insulin A and B chains linked by connecting or C-peptide. Proinsulin is packaged into small granules within the Golgi complex, which then migrate towards the cell surface. As the granules mature, proteases split proinsulin into equal amounts of insulin and C-peptide, allowing the insulin molecule, consisting of A and B chains linked by two disulfide bridges, to assume its active configuration. The resulting mature insulin composed of the A chain with 21 amino acids and the B chain with 30 amino acids as shown in (Figure 1.1) and with a molecular weight of 5800 g mol^{-1}. Both chains are held together by two disulphide bonds. Another disulphide bond is internal within the A chain itself (Owens, 2002).

Following biosynthesis, insulin is stored as crystalline zinc-bound hexamers in vesicles within the pancreatic β-cells from which secretion occurs in response to elevated blood glucose levels (Lemaire et al., 2012). Insulin has an isoelectric point (pI) of 5.3 and a charge of -2 to -6 in the pH range 7-11. Another intrinsic property of insulin is its ability to readily associate into dimmers, hexamers and higher-order aggregates. At the low concentrations found in the blood stream (< 10-3 μM), insulin exists as a monomer, which is its biologically active form (Chien, 1996).