Discovery of incretin hormones and incretin effect was postulated in the early 20th Century, when Murce administered duodenal extract to diabetic patients and demonstrated reduction in glycosurea. However, the specific substance responsible for action of incretin remained elusive for a long time. With discovery of insulin and later of its available assays, studies were carried out by measuring insulin levels in blood after administering an intravenous load of glucose and comparing it with oral ingestion of the same. Surprisingly insulin levels were higher after oral ingestion of glucose than after I.V administration. It became clear that a sequence of physiological responses is activated following meal intake. The G.I. tract has a significant role in absorption, digestion and assimilation of ingested nutrient with Incretins, mainly GIP and GLP. Purification and characterization of the first incretin GIP-(Glucose dependent insulinotropic polypeptide) was done in 1973. Studies on GIP indicated that another gut-derived biological active factor also played a significant role in glucose metabolism.

The second peptide with incretin activity, a glucagon like peptide (GLP-1) was discovered in 1987. Both GIP and GLP-1 are extremely short-acting. Plasma half-life of GLP is 1-2 minutes. This rapid inactivation is due to a ubiquitous enzyme, dipeptidyl peptidase-IV (DPP-IV). Hence the search was on for a synthetic GLP-1 and an inhibitor of DPP-IV enzyme.

In 1992, J. Eng, J P Raufmann and co-workers identified a breakthrough in the most unusual place, after considerable research. They found a peptide in the venom of a poisonous lizard- the ‘Gila monster’ (Heloderma suspectum), seen in Arizona and Mexican deserts. The peptide was mainly in the saliva of this lizard and was called extendin-4. It is a potent agonist at the GLP-1 receptor of insulin secreting beta cells in pancreas and remains effective for much longer than human GLP-1. Later it was renamed Exenatide and after clinical trials by pharmaceutical company Lilly it was approved by FDA in 2005 for treatment of type-2 diabetes. Exenatide offered further advantage of acting on the brain to reduce sensation of hunger thus aiding weight loss.

The pharmaceutical giant Merck began to investigate DPP-IV enzyme inhibitors by using computer mathematical models. The outcome was sitagliptin, the first DPP-IV inhibitor to be approved by FDA (2006) for type-2 diabetes. The manufacturing rights are with M S D. The importance of computer simulation in chemistry was recognized and 2013 Nobel Prize for chemistry was won by Michael Levitt, Martin Karplus and A. Warshel.

There has been some concern that both exetinide and sitagliptin may present risk of acute pancreatitis. This is because of the observation that the Gila monster eats only 5-10 times a year, and between meals its metabolism is very slow, and digestive system becomes dormant. When it eats, the GLP-1-like hormone in its saliva causes its pancreas to grow very quickly as much as 50%. Similar pancreatic growth has been observed in rodents who received exenatide and sitagliptin. Hence these drugs have come under increasing scrutiny. Further studies on this aspect are progressing, with many newer gliptins appearing in the market.