Insulin systems for peroral peptide drug delivery [24,

Insulin DeliverySeveral alternative routes of insulinadministration have been developed, such as pulmonary, nasal, buccal, oral, rectal, ocular, transdermal, vaginal, and intrauterine 16. Oral insulin delivery has been expected tobe more expedient and to enhance patient adherence. More importantly, oralinsulin absorption closely imitates insulin secretion under physiologicalconditions. Thus, it may exercise direct effects on hepatic glucose productionand reduce the risk of hypoglycemia associated with peripheral insulininjection 17. Oral insulin delivery remains challenging, however, and numerous attempts have failed to improve outcomes, includingliposomes, microcapsules, beads, hydrogels, and chemical modifications of themolecule 18. Nonetheless, augmented research efforts inthe past decades evidently demonstrate the possibility of developing polymericstrategies for oral insulin therapy.

Even though some of these methods haveshown low bioavailability of insulin and exhibit several negative effects suchas irritation of the intestinal mucosal membrane and damage of the membranebarrier, yet few strategies including copolymeric hydrogel microparticle ofpoly(methacrylic acid) joined with poly(ethylene glycol) P(MAAg- EG) havedemonstrated 19-22 enhancement of oral insulin absorption inanimal experiments up to 4. 2% bioavailability in addition to their ability toprotect insulin from the enzymes as well as adhesive features on the mucusmembrane. In a recent study by Sonaje et al. 23 the highest achievement of insulinbioavailability was demonstrated in animal diabetic models. They was prepared apH-sensitive nanoparticle (NP) system composed of poly(g-glutamic acid) andchitosan as a potential approach for the oral delivery of insulin 8. Dorkooshet al. 24 have

prepared a novel delivery systems basedon superporous hydrogel (SPH) and SPH composite (SPHC) polymers were used toimprove the intestinal absorption of insulin in healthy pigs.

These resultsindicate that the absorption of insulin was slightly increased usingSPH/SPHC-based delivery systems. Furthermore, a large variability was observed, probably due to physiological and metabolic changes during the experiments. Inconclusion, SPH/SPHC-based delivery systems are able to enhance the intestinalabsorption of insulin and are, therefore, considered as promising systems forperoral peptide drug delivery 24, 25.

A sustained injectable insulin deliverysystem of poly (?-amino ester)-poly (?-caprolactone)-poly (ethyleneglycol)-poly (?-caprolactone)-poly (?-amino ester) (PAE-PCL-PEG-PCL-PAE)pentablock copolymer as a pH -temperature-sensitive hydrogel was assessed byHuynh et al. The obtained results showed that hydrogel complex could besuggested the therapeutic potential for diabetic patients 26. In the same study, the novel pH-, ionicstrength and temperature- sensitive hydrogel was used for insulin delivery 27. The pH/thermosensitive polymeric beads basedpolymers of N-isopropylacrylamide (NIPAm), butyl methacrylate (BMA), andacrylic acid (AA) applied to release of insulin. The molecular weight (MW) ofthe polymers was affected upon the release rate of drug 28.

In another study, James et al. have preparedsmart polymeric as “ intelligent” delivery systems able to sustained release oftherapeutic macromolecules29. Amongst nanocarriers, polymericnanoparticles (NPs) have showed significant advantages for protein and peptidedrug delivery following oral, nasal,

pulmonary, parenteral, transdermal, andocular performances 30. PCL– PEG–PCL, chitosan (CS), and PLA NPs wasachieved higher insulin loading and employed to improve bioavailability andhypoglycemic activity of insulin via oral route 31, 32.

The chitosan-N-acetyl-L-cysteine (CS-NAC)NPs, and Hybrid poly-oligosaccharide NPs comprising of CS and cyclodextrinswere applied as nanocarriers for nosal insulin delivery 33, 34. Nanocarriers such as CS NPs has beensuggested as an excellent formulation for local and systemic delivery ofinsulin following pulmonary route 30, 35. The polymeric nanocarriers to insulindelivery have been using to increase the properties as solubility, bioavailability, and prolonged circulation times. 36.

Insulin-loaded acrylic hydrogels containingabsorption enhancers applied to rectal insulin delivery: in vitro and in vivostudy 37.