2. LITERATURE REVIEW

Amani Elsayed et al.\textsuperscript{1} have found Formulation and characterization of an oily-based system for oral delivery of insulin. The present work explored the possibility of formulating an oral insulin delivery system by combining the advantages of nanoencapsulation and the use of oily vehicle. The parameters affecting formulation such as association efficiency were characterized. The preparation was evaluated for its chemical, physical and biological stability. Insulin was protected from gastric enzymes by incorporation into lipid-based formulation. The results of RP HPLC and ELISA indicated that insulin was able to withstand the preparation procedure. It was also biologically active and stable as demonstrated by the remarkable reduction of blood glucose levels of the STZ-diabetic rats after oral administration of the preparation. Moreover, hypoglycemic effect of nanoparticles administered orally was sustained for a longer period of time compared to the subcutaneous injection.

Fude Cui et al.\textsuperscript{2} investigate Biodegradable nanoparticles loaded with insulin–phospholipid complex for oral delivery: Preparation, in vitro characterization and in vivo evaluation. Biodegradable nanoparticles loaded with insulin–phospholipid complex were prepared by a novel reverse micelle–solvent evaporation method. The effects of key parameters such as polymer/SPC weight ratio, organic phase and polymer type on the properties of the nanoparticles were investigated. Spherical particles of 200 nm mean diameter and a narrow size distribution were obtained under optimal conditions. The drug entrapment efficiency was up to 90%. Intragastric administration of the 20 IU/kg nanoparticles reduced fasting plasma glucose levels to 57.4% within the first 8 h of administration and this continued for 12 h. PK/PD analysis indicated that 7.7% of oral bioavailability relative to subcutaneous injection was obtained.

M.R. Rekha et al.\textsuperscript{3} established Synthesis and evaluation of lauryl succinyl chitosan particles towards oral insulin delivery and absorption. In this work a novel chitosan derivative, lauryl succinyl chitosan (LSC) was developed for the purpose of evaluating its applications towards oral peptide delivery system. Human insulin was used as the model protein drug and the release kinetics was studied at gastrointestinal pH. The presence of
succinyl carboxyl groups had inhibitory effect on the release kinetics of insulin at pH 1.2 minimizing up to about 8.5±0.45% in two hours. The mucoadhesive capacity was established ex vivo using the jejunum of rat intestine. The results demonstrated that the modified chitosan with both hydrophilic (succinyl) and hydrophobic (lauryl) moieties had improved the release characteristics, mucoadhesivity as well as the permeability of the insulin compared to the native chitosan particles.

**Florence Delie et al.**[^1] decided Polymeric Particulates to Improve Oral Bioavailability of Peptide Drugs, Oral administration remains the most convenient way of delivering drugs. Recent advances in biotechnology have produced highly potent new molecules such as peptides, proteins and nucleic acids. Despite sophisticated new delivery systems, the development of a satisfactory oral formulation remains a challenge. Increasing attention has been paid to their potential use as carriers for peptide drugs for oral administration. This article reviews the most common manufacturing methods for polymeric particles and the physiology of particle absorption from the gastrointestinal (GI) tract. In a second part, the use of polymeric particulate systems to improve the oral absorption of insulin is discussed.

**J. Liao et al.**[^5] resulted Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of an Improved Oral Insulin Solid Formulation in a Rat Model, To evaluate the PK / PD effects and the bioavailability of an improved oral insulin solid formulation. The improved oral insulin solid formulation was formulated with insulin and a DA at a specific insulin/DA ratio and further processed. The formulation was loaded in capsules and tested in fasted Sprague Dawley rats with a body weight of approx. 350 grams through oral administration (n=10). Insulin/DA blend in capsule and a solution formulation with the same insulin/DA ratio were also tested respectively for comparison. The absolute bioavailability of insulin was then calculated.

**Deepti Jain et al.**[^6] prepared Eudragit S100 Entrapped Insulin Microspheres for Oral Delivery, Microspheres were prepared using water-in oil-in water (w/o/w) emulsion-solvent evaporation technique with polysorbate 20 as dispersing agent in the internal aqueous phase and PVA/PVP as stabilizer in the external aqueous phase. PVA-stabilized microspheres having maximum drug encapsulation, released 2.5 % insulin at pH 1.0 in 2

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hours. In phosphate buffer (pH 7.4) microspheres showed an initial burst release of 22% in 1 hr with additional 28% release in the next 5 hrs. The release of drug from microspheres followed Higuchi kinetics. Oral administration of PVA stabilized microspheres in normal albino rabbits (equivalent to 6.6 I.U. insulin /kg of animal weight) demonstrated a 24% reduction in blood glucose level, with maximum plasma glucose reduction.

S. Lee et al. have believed A new drug carrier, Na-deoxycholyl-L-lysyl-methylester, for enhancing insulin absorption in the intestine, The development of an orally active insulin formulation will offer great advantages over conventional injectable insulin therapy in the treatment of patients with diabetes mellitus. Since insulin absorption in the intestine is restricted by the natural physiological characteristics of insulin, we developed a small synthetic compound, Na-deoxycholyl-L-lysyl-methylester (DCK), as an insulin carrier to enhance oral delivery. Conclusions/interpretation: The results of this study demonstrate that the insulin/DCK formulation can be absorbed in the intestine and that it is biologically efficacious. We therefore suggest that this oral formulation could be used as an alternative to injectable insulin with enhanced clinical effects.

Lutz Heinemann et al. talk Oral Insulin and Buccal Insulin: A Critical Reappraisal

Despite the availability of modern insulin injection devices with needles that are so sharp and thin that practically no injection pain takes place, it is still the dream of patients with diabetes to, for example, swallow a tablet with insulin. The aim of this review is to critically describe the different approaches that are currently under development. Optimal coverage of prandial insulin requirements is the aim with both routes of insulin administration (at least with most approaches). The speed of onset of metabolic effect seen with some oral insulin approaches is rapid, but absorption appears to be lower when the tablet is taken immediately prior to a meal.

Akhlesh Kumar Jain et al. developed Effective insulin delivery using starch nanoparticles as a potential trans-nasal mucoadhesive carrier, Mucoadhesive nanoparticles (NPs) could be an exciting prospect for trans-nasal insulin delivery as they have higher surface area to cover highly vascularised nasal absorptive area providing a greater concentration gradient; hence the present study makes an attempt in this regard. NPs of epichlorohydrin emulsion were further optimized with variable crosslinking to evaluate the
effect of degree of crosslinking on in vivo performance. Formulation of EE–NPs with Na glycocholate showed a superior hypoglycemic action compared to other NPs formulations containing the former and lysophosphatidylcholine as permeation enhancers.

**Dong Yun Lee et al.**\(^{10}\) created lipophilic complexation of heparin based on bile acid for oral delivery) Oral delivery of heparin will offer great advantages over injectable heparin therapy in the treatment of patients with deep vein thrombosis. Since heparin absorption in the intestine is restricted due to its physicochemical properties, we designed a bile acid derivative, cationic deoxylcholylethylamine (DCEA), to be complexed with anionic low molecular weight heparin (LMWH). Complexation between LMWH and DCEA was saturated above 1:10 molar ratio and improved lipophilicity of LMWH. The LMWH/DCEA complex was completely solubilized in 80% propylene glycol solution. The oral absorption of LMWH in rats was proportional to the molar ratio of DCEA and the administered dose of complex. This study demonstrates the feasibility of oral heparin delivery using the cationic DCEA for chronic administration in clinical trials as an effective therapy.

**P Pozzilli et al.**\(^{11}\) prepared oral spray insulin in patients with type 1 diabetes: Comparison with subcutaneous insulin, Insulin therapy by subcutaneous injection is the standard treatment for patients with Type 1 diabetes. The study protocol was designed to compare blood glucose, insulin and C-peptide levels in 9 patients treated with subcutaneous or oral insulin on two consecutive study mornings. Patients were sampled up to 4 hours to evaluate blood glucose, plasma insulin and C-peptide. No basal insulin was administered to patients in the morning of the test. In 3 male patients affected by Type 1 diabetes (aged 28, 34, 35 years) pre-meal oral insulin treatment was prolonged for two consecutive days. In these patients we blood glucose levels were monitored throughout the day for three consecutive days by the recently developed glucose sensor monitoring system. There were no significant differences in the blood glucose, insulin and C-peptide levels measured after treatment with subcutaneous insulin or oral insulin.

**B. Sarmento et al.**\(^{12}\) investigated Alginate/Chitosan Nanoparticles are Effective for Oral Insulin Delivery to evaluate the pharmacological activity of insulin-loaded alginate/chitosan nanoparticles following oral dosage in diabetic rats. The insulin
association efficiency was over 70% and insulin was released in a pH-dependent manner under simulated gastrointestinal conditions. Confocal microscopic examinations of FITC-labeled insulin nanoparticles showed clear adhesion to rat intestinal epithelium, and internalization of insulin within the intestinal mucosa. Conclusion. The results indicate that the encapsulation of insulin into mucoadhesive nanoparticles was a key factor in the improvement of its oral absorption and oral bioactivity.

**Bruno Sarmento et al.** prepared Oral insulin delivery by means of solid lipid nanoparticles. The aim of this work was to produce and characterize cetyl palmitate-based solid lipid nanoparticles (SLN) containing insulin, and to evaluate the potential of these colloidal carriers for oral administration. SLN were prepared by a modified solvent emulsification evaporation method based on a w/o/w double emulsion. The particle size, zeta potential and association efficiency of unloaded and insulin-loaded SLN were determined and were found to be around 350 nm, negatively charged and the insulin association efficiency was over 43%. After oral administration of insulin-loaded SLN to diabetic rats, a considerable hypoglycemic effect was observed during 24 hours. These results demonstrated that SLN promote the oral absorption of insulin.

**Yu-Hsin Lin et al.** have found Preparation and Characterization of Nanoparticles Shelled with Chitosan for Oral Insulin Delivery, Nanoparticles (NPs) composed of chitosan (CS) and poly(ζ-glutamic acid) (ζ-PGA) were prepared by a simple ionic-gelation method for oral insulin delivery. Fourier transform infrared (FT-IR) spectra indicated that CS and ζ-PGA were ionized at pH 2.5-6.6, while X-ray diffractograms demonstrated that the crystal structure of CS was disrupted after it was combined with ζ-PGA. The diameters of the prepared NPs were in the range of 110-150 nm with a negative or positive surface charge, depending on the relative concentrations of CS to ζ-PGA used. The NPs with a positive surface charge (or shelled with CS) could transiently open the tight junctions between cells and thus increased the paracellular permeability. After loading of insulin, the NPs remained spherical and the insulin release profiles were significantly affected by their stability in distinct pH environments. The in vivo results clearly indicated that the insulin-loaded NPs could effectively reduce the blood glucose level in a diabetic rat model.
2.1 References


