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Strategies for Effective Oral Insulin Delivery with Protamine Coated Proliposomes Encased in Eudragit S100 Coated Capsule: A Review

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Review Article

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ABSTRACT

Parenteral administration of insulin is associated with serious flaws like potential pain or discomfort for the patient, local allergy, abscess at the injection site, lipoatrophy (localized loss of fat tissue) and anaphylaxis. In addition, industrial issues like physical and chemical changes during manufacturing, shipping, storage and administration also influence the clinical potency of insulin. Hence, proliposomes followed by encasing in eudragit S100 coated capsule for oral administration has been widely studied in oral insulin delivery to address pharmaceutical, physiological and industrial issues. This review focuses on advancement in the synthesis of protamine coated proliposomes of recombinant human insulin encased in Eudragit S100 coated capsule for efficient oral insulin delivery. Alterations to protect insulin from the cruel acidic environment of the gastro-intestinal (GI) tract are defined. Chemical barriers for example, the acidic gastric pH and the presence of proteolytic enzymes in the stomach and intestine restrain the effective absorption of external insulin within the GI tract.

INTRODUCTION

Diabetes mellitus is a metabolic disorder and major health issue of almost all the countries. Insulin is a therapeutically active protein peptide hormone and utilized in the treatment of diabetes mellitus [1,2]. Presence of proteolytic enzyme and gastric acid in gastrointestinal tract causes degradation of insulin [3]. Insulin is mainly administered via the subcutaneous route, which has some disadvantages like local allergy, infection, injection site abscess and lipoatrophy is common and is occur because of repeated injection of insulin at same site. Anaphylaxis is very rarely seen and requires desensitization with gradually increasing dose of insulin, local pain, itching, lipodystrophy, inconvenience of multiple injections, hypoglycaemia because of overdose of hyperinsulinemia [4-6].

Next to pharmaceutical issues, industrial concerns like physical and chemical changes during manufacturing, shipping, storage and administration adversely alter the drug potency and safety. Insulin is well known to lose activity as a result of protein aggregation upon agitation at high temperature. This may limit the shelf life and make storage and transport less convenient and more expensive [7-9]. Ultimately, oral delivery of insulin is one of the alternatives to gain clinical bioavailability in the systemic circulation due to high patient compliance and safety issues [3,10,11]. Despite the worthwhile outputs of administration of insulin through oral route, proteolytic enzymes, cruel acidic conditions and low intestinal epithelial permeability hamper the stability and bioavailability of peptide [1,11-13].

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Researchers have been attempting to address both pharmaceutical and industrial issues through different novel excipients [14-16].

CHALLENGES TO ORAL INSULIN DELIVERY

Diabetes mellitus is a metabolic disease and major health issue of almost all the countries [17-19]. The prevalence of diabetes for all age group worldwide predicted to be 2.8 percentage in 2000 and 4.4 percentage in 2030 [20]. Insulin is a therapeutically active protein of great interest due to its broad use in the management of diabetes mellitus [1]. Hence, insulin is generally recommended by the physicians to normalize the blood glucose level in diabetic patients. Insulin is a polypeptide hormone normally restricted to subcutaneous administration because it is easily hydrolyzed in acidic conditions of stomach, degrades by proteolytic enzyme in gastrointestinal tract (GI) and metabolised by enterohepatic circulation [1,21,22].

Insulin structure consists of disulfide bond that readily denatures in cruel conditions of stomach [23-25]. Furthermore, physical and chemical changes during manufacturing, shipping, storage and administration adversely alter the drug potency and safety during industrial scale-up of conventional insulin dosage form. Recently, aggregation has emerged as an industrial issue related to conventional insulin parenteral formulation underlying multiple deleterious effects including loss of efficacy, altered pharmacokinetics, deprived stability and product shelf life [26-29]. However recent studies showed that, insulin loaded protamine sulphate coated proliposomes that will be further encased in eudragit S100 coated capsule for oral route insulin administration address both pharmaceutical and industrial issues [30,31].

PROLIPOSOMES FOR INSULIN DELIVERY

Different carrier system is used for insulin delivery such as Hyderogels, Liposomes, Nanospheres, Nanocubicls [24]. Liposomes being among the most studied particulate carrier systems and have potential in enhancing oral bioavailability of protein and peptide drugs [32-35]. Liposomes show controlled release and increased solubility but have affinity to aggregate or fuse and are more susceptible to hydrolysis or oxidation.

Recent studies showed that Proliposomes offer an elegant alternative to conventional liposomal formulations [36-38]. Proliposomes are the dry powder nanovesicles comprising water soluble carrier particles coated with phospholipids and can be reconstituted to form liposomal dispersion on brief agitation in aqueous medium [38]. Meritoriously, proliposomes offer several advantages over conventional drug delivery systems. Proliposomes reported to have greater efficacy, less toxicity, high stability and controlled drug release properties [39,40].

PASSAGE THROUGH THE HARSH ENVIRONMENTAL CONDITION OF STOMACH

The harsh condition of gastrointestinal tract (GIT) undergoes enzymatic degration of insulin by pancreatic proteolytic enzymes such as trypsin and α-chymotrypsin [41-43]. Eudragit S100, a pH sensitive smart polymer, provides better protection to peptide from enzymatic degradation and allow vehicle to release most of the entrapped therapeutic component in intestinal milieu [30,44-46].

INTESTINAL TRANSPORT OF INSULIN

Insulin has low permeability through intestinal mucosa. Hence, protamine sulphate coated proliposomes may promote the delivery of insulin through intestinal membrane [32]. Eudragit S100 coated capsule containing insulin loaded protamine sulphate modified proliposomes are easily dissolves at intestinal pH and help to release insulin in the terminal ileum [48-50].

CONCLUSION

In recent years numerous studies focused on different administration routes and insulin delivery system. Recent studies showed that insulin loaded protamine sulfate coated proliposomes encased in eudragit S100 coated capsule would exhibit superior bioavailability, high stability and improved patient compliance with strong marketing potential.

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