EXPERT OPINION

Colon targeting: an emerging frontier for oral insulin delivery

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Subcutaneous administration of insulin is associated with several limitations such as discomfort, local pain, irritation, infections, immune reactions and lipoatrophy as well as lipohypertrophy manifestations at the injection site. To overcome these drawbacks, enormous research is currently going on worldwide for designing of an alternative noninvasive route of administration. Pulmonary and oral route seem to be the most promising ones, with respect to the market value. However, after the letdown by pulmonary delivery of insulin, oral colon targeted delivery of insulin has gained tremendous interest among researchers. Although bioavailability remains a challenge for oral colon specific delivery of insulin, the employment of protease inhibitors, permeation enhancers and polymeric delivery systems have proved to be advantageous to overcome the said problem. This Editorial article is not intended to offer a comprehensive review on drug delivery, but shall familiarize the readers with the strategies employed for attaining non-erratic bioavailability of insulin, and to highlight some of the formulation technologies that have been developed for attaining oral colon-specific delivery of insulin.

Keywords: colon targeting, Eudragit, insulin, particulate drug delivery, permeation enhancers, protease inhibitors

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1. Introduction

Diabetes mellitus, a major endocrine disorder, is characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism that result in defects in insulin secretion, insulin action or both. Diabetes mellitus is the sixth most common cause of death in the world. In 2012, more than 371 million people had diabetes, out of which 4.8 million people died due to the disease. More than 471 billion USD were spent on health care for diabetes, yet half of the people with diabetes were undiagnosed [1]. People with type 1 diabetes mellitus do not produce enough insulin to sustain life and become dependent on exogenous insulin for survival. By contrast, people with type 2 diabetes are not dependent on exogenous insulin for survival. Over time, many of these individuals will show decreased insulin production, thereby requiring exogenous insulin for adequate blood glucose control, especially during times of stress or illness. Governments and various health care providers around the world are investing in health education, diagnosis and treatments for this chronic disorder. Consequently, it is one of the largest sectors in the global health care industry in terms of market value.

Since the discovery of insulin, it is delivered to diabetic patients exclusively through the subcutaneous route. The usual duration of action is relatively short (i.e., 4 to 8 h) and therefore, two to four daily injections are required for proper control of severe diabetic conditions. Although the parenteral route is satisfactory in terms of efficacy, frequent administration leads to discomfort, local pain, irritation, infections, immune reactions and lipoatrophy as well as lipohypertrophy manifestations at the injection site. Further, subcutaneous insulin results in fluctuating blood glucose levels, which is a major risk factor for development of long term micro- and

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macrovascular complications that are the leading cause of morbidity and mortality [2].

Oral route is regarded as the most preferred route of administration because of its well-established acceptability, cost-effectiveness benefits and certain advantages such as higher compliance, greater convenience, and reduced risk of cross infection and needlestick injuries. Due to these reasons, oral drug delivery systems continue to dominate majority of the market. Furthermore, it holds the biggest presence in the overall drug delivery market, with about 52% share. It is expected to reach 92 billion USD by 2016 [3]. Although advantageous, the oral route is not suitable for the administration of protein and polypeptide drugs popular today. This is because they are highly susceptible to digestive enzymes present in the gastrointestinal tract (GIT), and thus they are poorly absorbed and possess limited ability to be transported across the intestinal epithelial barrier. Even though oral delivery involves severe stability and permeability issues, it has recently gained tremendous interest, especially after the letdown by pulmonary delivery of insulin.

Moreover, oral delivery seems to replicate the physiological fate of insulin more closely as compared to other routes of administration. Before reaching colonic region for systemic absorption (circulation), insulin has to travel intact through stomach and small intestine, without losing its integrity and conformation (**Figure 1A**). After the absorption of insulin from the colon, it is transported to the liver vial portal circulation, where it could largely be extracted as occurring on incretion by β-cells from the pancreas (**Figure 1A**). There are very few drugs that have beneficial effect after hepatic first-pass metabolism, insulin being one of them [4]. In case of parenteral administration, there occurs initial hyperinsulinemia, which is associated with risk of hypoglycemia, atherogenesis, lipogenesis, weight gain and possible development of insulin resistance. However, due to hepatic first-pass metabolism in case of oral administration, there might be absence of peripheral hyperinsulinemia, and insulin directly reaches the liver and regulates carbohydrate metabolism. In addition to this, other benefits include improved dosing convenience, which increases patient compliance and thereby high intensive insulin regimens can be given [2].

2. Strategies employed for attaining non-erratic bioavailability of insulin

Oral administration of insulin depicts low bioavailability due to its large size, hydrophilicity, susceptibility to enzymatic degradation and poor absorption characteristics. The use of permeation enhancers, protease inhibitors and polymeric delivery systems are some of the recent strategies being investigated for orally delivered proteins. Although most of these strategies lead to encouraging results, low bioavailability remains a problem. Combination of these strategies could overcome the above-mentioned problem [5].

2.1 Protease inhibitors (Biochemical factor)

Similar to upper GIT, the colonic region also possess biochemical barriers that include residual soluble proteases of pancreatic origin and enzymes produced by the resident micro-organisms and derived from sloughed enterocytes. A variety of exo- and endopeptidases are present at the brush border membrane, among which exopeptidases are more prominent in terms of N-terminal cleavage activity [2]. Cytosolic and lysosomal enzymes are responsible for attack in intracellular compartment. The type of protease inhibitor to be used depends on the target enzyme required to be inactivated, for example, for inactivation of trypsin and chymotrypsin, aprotinin has been effectively used since long; all pancreatic endopeptidases (though not exopeptidases) were inhibited by Bowman–Birk inhibitors and soybean trypsin [6]. Proteases may also be inhibited indirectly by shifting the pH value out of the optimum range for the enzyme activity by using pH modifiers [7].

2.2 Permeation enhancers (Biophysical factor)

The semisolid content of the colonic lumen is the most common biophysical factor that prevents the direct contact between the drug and absorptive mucosa. Mucus and glycocalyx act as the subsequent physical barrier that hinders the diffusion of macromolecules toward intestinal wall due to interactions with mucin and cell-bound components or due to inherent solubility and/or diffusivity constraints. At the apical mucosal surface, the macromolecules neither get permeated through transcellular route (because of their hydrophilic nature and high molecular weight) nor by paracellular route (diffusion of molecules with > 200 Da mass is unlikely). The other viable modes of transport left over are carrier-mediated transport and endocytosis. The absorbed molecule gets released into the basolateral compartment by transcytosis process [2].

Permeation enhancers are the key tools employed to overcome the biophysical barriers. They are generally amphiphilic compounds, viz., glycerides, acylcarnitines, alkyl-saccharides, chelating agents, surfactants, bile salts, salicylates and fatty acids. **Figure 1B** represents some of the common mechanisms through which permeation enhancers increase the absorption of macromolecules. The permeation enhancers should produce prompt, transient and fully reversible effects, regardless of the mechanism involved in enhancement of absorption. On the contrary, issues such as permanent mucosal damage and increased permeability to pathogens or potentially toxic substances, lack of prompt and full recovery and risks arising from intensified repair processes need to be addressed [8,9].

2.3 Particulate drug delivery systems

As discussed earlier, for a successful delivery of macromolecules to the systemic circulation, the systems should provide protection against enzymatic degradation and should provide high transfer of drugs across the epithelium mucosa. As particulate drug delivery systems fulfill these requirements;

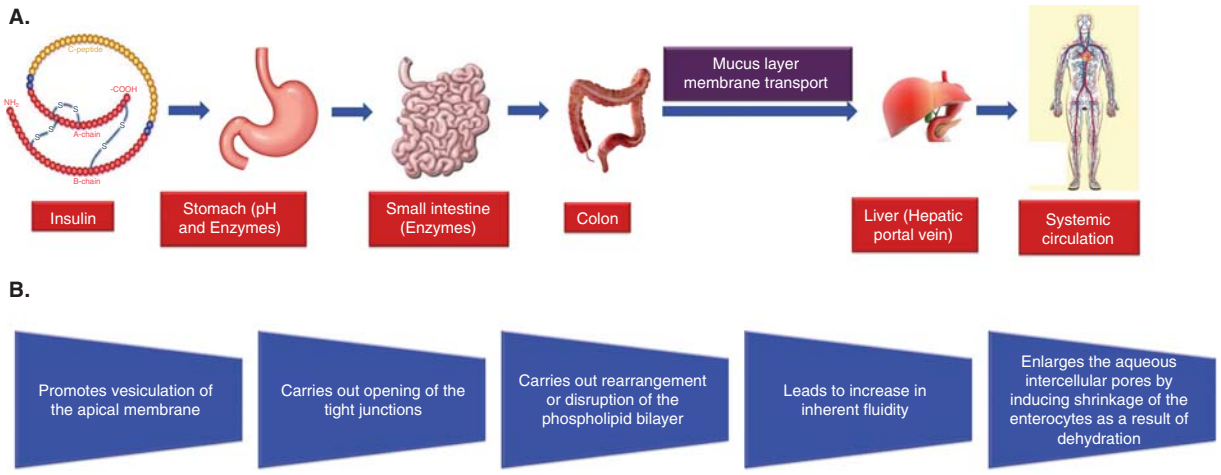

Figure 1. Pathway depicting delivery of insulin to the systemic circulation from oral colon-specific delivery system (**A**) and mechanism of permeation enhancers (**B**).

Table 1. Ideal characteristics of insulin carrier.

Should deliver an accurate amount of insulin with reproducible results
The polymeric particle should remain intact and should provide protection against the harsh external conditions of GIT (GI enzymes and pH gradients)
Should not interfere in the absorption or uptake of insulin by the intestinal wall
Should be safe for oral administration
The encapsulation process should not affect physicochemical and biological characteristics of insulin
Should retain the physiological activity during the encapsulation process and release of insulin
Should provide prolonged intestinal residence time to enhance the absorption of drug
Should contribute in increasing the permeability of insulin through the intestinal membrane

nanoparticles, lipid-based drug delivery systems (e.g., microemulsions, liposomes and solid lipid nanoparticles) and hydrogels and microspheres have been evaluated for oral delivery of macromolecules [10].

In the past decade, micro/nano-particulate systems for oral insulin delivery have gained tremendous interest among researchers. Both biodegradable and nonbiodegradable polymers have been investigated. As such, nonbiodegradable polymers are toxic and are difficult to remove from the body; they are not much employed for the oral delivery of insulin. On the contrary, a biodegradable polymer (or polymeric particles) forms a shield that encapsulates and protects the drug from the severe external conditions and further enables their uptake by enterocytes. Once absorbed, the polymeric particles will get degraded slowly (the degradation of polymeric system solely depends on its nature), hence providing a prolonged release of drug. The uptake of polymeric particles by the intestinal wall depends on the nature of the polymer, its surface charge and particle size. Further, the physicochemical properties, drug release characteristics and biological behavior of polymeric particles are some of the factors that can be tailored easily. **Table 1** represents some of the ideal characteristics that a polymeric carrier must meet for successful delivery of insulin [5].

3. Oral colon delivery of insulin

After the failure of pulmonary delivery of insulin, the colon has become one of the potential sites for systemic delivery of therapeutic proteins and peptides. The advantages offered by colon as a site for insulin delivery are represented in **Figure 2**. The technologies that have been developed for colonic delivery of insulin are summarized in **Table 2** (to understand the execution of developed systems of insulin for colon targeting, the readers are requested to have thorough knowledge pertaining to different approaches used for colon targeting [11-13]).

4. Expert opinion

Currently, enormous research is going on worldwide for designing of oral insulin formulation. A large amount of time and money have been invested in this field. Some achievements obtained from this research include in-depth knowledge and understanding of the challenges and constraints and suggestive measures to be taken to overcome them. Although tremendous research is being conducted at academic as well as industrial level for oral insulin delivery, the following are certain major constraints that still exist:

i) The developed oral insulin systems have not shown sufficient bioavailability.

Figure 2. Advantages offered by colon as a potential site for insulin delivery.

ii) The methods employed for the development of oral formulation are not productive commercially and scalability remains a challenge.

iii) The pharmacological evaluations do not involve long-term study or continuous administration of insulin; rather, a single dose study with pharmacokinetic parameters estimation is reported in majority of the research papers.

iv) Glycated hemoglobin levels (HbA1c), which is a better marker for glucose control, is not reported.

v) Also very few publications report data pertaining to clinical trials.

Table 2. Systems developed for achieving colon-targeted delivery of insulin.

Approach	Type of dosage form	Description	Strategy applied (protease inhibitor and/or permeation enhancer)	Refs.
pH-dependent systems	Enteric coated capsule	The system consists of insulin filled into small, soft gelatin capsules coated with polyacrylic polymer (Eudragit) having pH-dependent properties. The capsules were filled with 8 units (u) of porcine insulin and 20 mg of surfactant mixture (sodium laurate: cetyl alcohol 2: 8) in arachis oil, and were coated with mixtures of various ratios of Eudragit RS, L and S.	Cetyl alcohol Sodium laurate	[14]
	Enteric coated capsule	Crystalline beef insulin was administered orally in capsules composed of a methacrylic acid copolymer, which prevents breakdown of insulin by enteric and pancreatic peptidases.	5-Methoxysalicylic acid Sodium lauryl sulfate Aprotinin Sodium taurocholate	[15]
	Enteric coated capsule	Formulation development was undertaken to target release utilizing Eudragit S100 enteric coating and decrease gastrointestinal transit time comparing two bioadhesive polymers (chitosan and Carbopol 934). Salicylate microspheres incorporated in enteric and non-enteric formulations with chitosan or Carbomer (Carbopol 934) were tested for sustained delivery in the lower GIT using rat and dog animal models. Optimized formulations were designed for porcine insulin, which was then tested in the non-diabetic dog model for bioavailability and pharmacological response. Improved bioavailability for the enteric coated oral insulin formulation was observed in the dog model with prolonged decrease in plasma glucose.	Sodium glycocholate Disodium ethylenediaminetetraacetic acid (Na_2EDTA) Aprotinin Carbopol934	[16]
	Enteric coated microspheres	These microparticles were designed to provide pH-sensitive and controlled release properties by combining a release-retarding lipid core and a pH-sensitive coating. Lipid cores were prepared by solvent evaporation method, which was then encapsulated within a pH-sensitive polymer, the hydroxypropylmethylcellulose acetate succinate (HPMC-AS), by adapting the aqueous solvent extraction technique.	Chitosan	[17]
	Microparticulate system	Insulin-loaded HPMC-AS microspheres were prepared	Bacitracin, Sodium oleate	[18]
Time-dependent systems	Tablets	Insulin-loaded tablets coated with HPMC were prepared	Sodium glycocholate Camostat mesilate	[19]
pH and time–di-dependent systems	Enteric coated capsule	Microemulsions, used as a vehicle for insulin, were gelled using Cab-O-Sil, and filled into gelatin capsules pretreated with formaldehyde vapor. The capsules were coated with Eudragit NE 30 D, Eudragit S100 and cellulose acetate phthalate polymers of pH-dependent and time-controlled release mechanisms. An *in vivo* crossover study in beagle dogs was carried out employing the following treatments: i.v. insulin, p.o. insulin microemulsion and colonic release capsule dosage form without insulin (CRC), were used as controls, a colonic release capsule dosage form with insulin	Sodium laurylsulfate Aprotinin	[20]

Table 2. Systems developed for achieving colon-targeted delivery of insulin (continued).

Approach	Type of dosage form	Description	Strategy applied (protease inhibitor and/or permeation enhancer)	Refs.
		(CRI) and additionally with sodium lauryl sulfate (CRIL) or aprotinin (CRIA) as sorption promoter and enzyme inhibitor, respectively. The pharmacological availability (PA) for the p.o. microemulsion, CRC, CRI, CRIL and CRIA were 2.1, 0.4, 5.0, 2.7 and 6.2%, respectively. Insulin release occurred throughout the GI tract, with the exception of the stomach. Tmax occurred at 6.4 h for CRIA; the majority of insulin is taken up after the colonic arrival time is reached in the dog (4 – 6 h). Duration of the reduction in blood glucose levels occurred for 14 h with the CRIA dosage form.		
	Enteric coated capsule	The system was designed by imparting a time-release function and a pH-sensing function to a hard gelatin capsule. The technical characteristics of the system are to contain an organic acid together with an active ingredient in a capsule coated with a three-layered film consisting of an acid-soluble polymer, a water-soluble polymer, and an enteric polymer.	–	[21]
Microflora activated systems	Multiparticulate system (pellets)	Peptide drugs were coated with polymers cross-linked with azoaromatic groups to form an impervious film to protect orally administered drugs from digestion in the stomach and small intestine.	–	[22]
	Azopolymer-coated gelatin capsule	Bovine crystalline insulin, mixed with an absorption enhancer, was loaded into gelatin capsules, which were then coated with an azopolymer designed to deliver the insulin in the upper colon. An *in vivo* study was carried out using pancreatectomized mongrel dogs. The coated capsules were administered orally after a pre-dose period of 1 h. Responses measured were plasma glucose, plasma insulin, hepatic glucose production rate, hepatic plasma flow rate and plasma glucagon-like immunoactivity (GLI). Control experiments, with capsules without insulin, produced small changes from 'pre-dose' values. Insulin-containing capsules, without the azopolymer coating, resulted in some early changes consistent with upper gastrointestinal absorption. Single oral doses (66 to 400 nmol/kg) of insulin in completely coated capsules produced peaks of portal plasma insulin and transient decreases in plasma glucose, hepatic glucose production, hepatic plasma flow and plasma GLI.	5-Methoxysalicylic acid	[23]
	Multiparticulate system (pellets)	Insulin and (Asu(1,7))eel-calcitonin loaded pellets coated with azoaromatic polymer were prepared. The intestinal absorption of insulin and (Asu(1,7))eel-calcitonin after oral administration of the azopolymer-coated pellets containing these peptides with camostat mesilate was evaluated by measuring the hypoglycemic and	Camostat mesilate	[24]

Table 2. Systems developed for achieving colon-targeted delivery of insulin (continued).

Approach	Type of dosage form	Description	Strategy applied (protease inhibitor and/or permeation enhancer)	Refs.
		hypocalcemic effects, respectively. A slight decrease in plasma glucose levels was observed following the oral administration of these pellets containing 12.5 IU of insulin compared with the same dose of insulin solution.		
	Tablets	Calcium pectinate matrix tablets with or without calcium pectinate compression coating were prepared. Calcium pectinate compression coated tablets containing insulin as a drug marker were administered orally to dogs. The delayed insulin absorption was related to a breakdown of the drug carrier in the dogs' large intestine.	Soybean trypsin inhibitor Sodium cholate	[25]
	Nanoparticulate delivery system	Insulin-loaded calcium pectinate nanoparticles were prepared by ionotropic gelation with calcium ions.	–	[26]
	Nanoparticulate delivery system	Insulin loaded nanoparticulate systems of chitosan, triethylchitosan and dimethyl-ethylchitosan were prepared by polyelectrolyte complexation method. *In vivo* studies in rats have showed enhanced colon absorption of insulin by using these nanoparticles compared to free insulin in diabetic rats. The insulin absorption from the rat's colon was evaluated by its hypoglycemic effect.	Non-associated chitosan, triethyl chitosan or dimethylethyl chitosan	[27]
pH and microflora-activated di-dependent systems	Enteric coated tablets	Lactulose-containing insulin loaded tablets with inner Eudragit E, intermediate HPMC and outer Eudragit L coatings were prepared. The system containing insulin and sodium glycocholate (CDS) was administered to dogs, and plasma glucose and insulin levels were then measured at 24 h after administration. For CDS, the Cmax in plasma glucose level was significantly higher than a reference formulation without sodium glycocholate. The pharmacological availability for CDS was not significantly higher than the reference formulation. In contrast, CDS with poly(ethylene oxide) as a gelling agent (CDSP) showed prolonged hypoglycemia effects. The pharmacological availability was 5.5% and significantly different from the reference formulation. The absolute bioavailability for CDS was 0.25%, and for CDSP it was 0.42%.	Camostat mesilate Na_2EDTA Sodium laurylsulfate Sodium glycocholate	[28]
	Enteric coated chitosan capsules	Insulin loaded chitosan capsules coated with enteric polymer were prepared. The intestinal absorption of insulin was evaluated by measuring the plasma insulin levels and its hypoglycemic effects after oral administration of the chitosan capsules containing insulin and additives. A marked absorption of insulin and a corresponding decrease in plasma glucose levels was observed following the oral administration of these capsules that contained 20 IU of insulin and sodium glycocholate (PA% = 3.49%), as compared to the capsules containing only lactose or only 20 IU of insulin (PA% = 1.62%). The hypoglycemic effect started from 8 h after the administration of chitosan capsules when the capsules entered the colon, as evaluated by the transit time experiments with chitosan capsules.	Bacitracin Aprotinin Sodium glycocholate Soybean trypsin inhibitor *N*-dodecyl-β,D-maltopyranoside Sodium oleate	[29]

To achieve high oral bioavailability of insulin, one has to apply strategies like modification of physicochemical property (lipophilicity and enzyme susceptibility) of the macromolecules, addition of novel functionality (e.g., receptor recognition or cell permeability) to the macromolecules, inhibition of degradation enzymes, increasing the membrane permeability and use of particulate delivery systems [10]. Further, it is now clear that the basic aim of developing oral insulin should be to obtain non-erratic bioavailability with oral formulation, which can then be combined with other dosage regimens. Besides this, a dose-dependent and reproducible formulation for successful oral insulin delivery is also required. Therefore, systematic evaluations of the matrix have to be carried out to make oral insulin delivery a reality. Further, unlike the case of small molecules, which can 'deliver themselves' with no need for any sophisticated strategy, only an advanced multifunctional formulation tailored to meet its particular pharmaceutical, biopharmaceutical and pharmacological requirements could ultimately be the key to a successful oral delivery of insulin. In view of the stringent quantitative and temporal dosing requirements as well as narrow therapeutic range of insulin, its delivery to the GI tract might fail to completely overcome the need for subcutaneous administration because of bioavailability constraints. An effective peroral formulation, however, could serve as a valuable support for parenteral insulin regimens. The consequent possibility of reducing the injective dosing frequency would offer major advantages in terms of limited adverse reactions at the injection site, decreased incidence of systemic hyperinsulinemia, improved patient compliance and more feasible accomplishment of near-normal blood glucose levels [2]. Last but not the least, one has to carry out an array of *in vivo* pharmacological studies to assess the long-term effects of oral insulin formulation, and thereby overcome the challenges provided by the oral route.

Declaration of interest

The author states no conflict of interest and has received no payment in the preparation of this manuscript.

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