Abstract
The subcutaneous injection of insulin for the treatment of diabetes mellitus can lead to patient non-compliance, discomfort, pain and local infection is a chronic metabolic health disease affecting the homeostasis of blood sugar levels in human beings. Oral route of drug delivery system has been the most widely accepted means of drug administration other than invasive drug delivery systems. For the development of an oral insulin delivery system, we have to focus on overcoming the various gastro-intestinal barriers for insulin uptake from the gastrointestinal tract. To overcome these barriers various types of formulations such as insulin conjugates, micro/nanoparticles, liposomes, hydrogel, capsule, and tablets are designed to deliver insulin orally. Various potential ways to administer insulin orally has been explored over years but a fluctuating level of insulin release has been recorded. A number of advancement has taken place in the recent years for understanding the needs of improved oral delivery systems of insulin. This review article concentrates on the challenges for oral drug delivery of insulin as well as various carriers used for the oral drug delivery of insulin and also provides the relevant information about the clinical tested formulations of oral insulin and its patents.

Keywords: Formulation technology, insulin, oral drug delivery, patient compliance.

Introduction
The effective treatment of diabetic person with insulin requires a route of administration that is painful to the patient. Although invasive routes are poorly acceptable by the diabetics but other noninvasive routes of administrations are highly expedient. Administration of drugs by oral route is the most acceptable route of administration, but it is difficult to deliver peptide and protein drugs by this route. Presystemic enzymatic degradation and poor penetration of the intestinal membrane are the main reasons for the low oral bioavailability of peptide and protein drugs. Oral bioavailability of insulin is below 1% so there is a big challenge to improve it up to 30%-50%. A number of polymers both biodegradable and non-biodegradable polymers have been studied for non-invasive delivery of insulin. Non-biodegradable polymers possess problems of toxicity, difficulty in evicition and also sustained release of insulin cannot be attained using these polymers. Biodegradable polymers favour the uptake of insulin through intestinal cells by shielding the encapsulated drug from the external harsh conditions. Biodegradable polymeric particles protect the peptide from the peptidases, enhancing uptake by enterocytes. Polymeric particles will slowly degrade after absorption depending on the nature of the polymer; provide a sustained and controlled release of the drug. Various strategies have to be implemented to maximize oral insulin bioavailability to overcome GI barriers, and to bring safe and effective oral dosage form to the market. In order to attain an ideal oral peptide drug delivery system, some alternates will be required to encapsulate the insulin. For the oral delivery of peptide and protein drugs, nanocarriers have shown great potential with improved pharmacokinetics and pharmacodynamics of insulin. Nano carriers or nanoparticles can stabilize these macromolecular drugs by providing insulation from the harsh GI conditions and accelerating their transport across the absorptive epithelia. The new strategies for products that are tried before include water-soluble, long-acting insulin derivative, [(2-Sulfo)-9-...
fluorenylmethoxycarbonyl] 3-insulin, vitamin B12-dextran nanoparticles, lipid nanoparticles and PEGylated calcium phosphate nanoparticles etc as oral drug delivery carriers for insulin.

**VARIOUS CHALLENGES TO ORAL INSULIN DRUG DELIVERY**

Absorption across GIT membrane

General route for absorption of drug molecules is the Paracellular and the transcellular route. Hydrophilic molecules having mol. Wt. less than 500 Da are absorbed by Paracellular route. The molecules having high molecular weight like insulin (about 6KDa) cannot absorb via this route. Absorption of insulin by transcellular route is restricted because of its molecular size, its charge, and its hydrophilicity. To increase the GI uptake of orally poorly absorbed insulin is their binding to colloidal particles that can safeguard the insulin from degradation in the GI tract and encourage the transport of poor-absorbable molecules into systemic circulation.

Presystemic enzymatic degradation

Pepsin is present inside the stomach as a group of aspartic proteases. Pancreatic proteases existing in small intestine comprising the serine endopeptidase (trypsin, a-chymotrypsin, elastase and exopeptidases, carboxypeptidase A, and carboxypeptidase B) which is accountable for the degradation of proteins. The order of enzymatic degradation of insulin in the small intestine is Duodenum > jejunum > ileum. Insulin can be available for absorption through GIT when the enzymatic attack is either diminished or overcome. Although insulin is not subject to proteolytic breakdown by brush border enzymes.

Poor Intestinal transport of insulin

The anatomy of insulin is very exquisite. Insulin is susceptible to oxidative damage when it react with amino acids. In other words we can say that insulin has low permeability via intestinal mucosa.

**Dosage form stability**

Proteins changes its conformation, size, shape, surface properties, and bioactivity upon development into different formulations. Changes in conformation, size, shape can be detected by use of spectrophotometric techniques, X-ray diffraction, differential scanning calorimetry, light scattering, electrophoresis, and gel filtration.(Figure 1)

**FEATURES OF AN ABSOLUTE ORAL INSULIN CARRIER**

An absolute carrier for insulin:
- should be pH sensitive.
- should provide a biocompatible and stable environment to ensure that the active part of insulin will remain biologically active after encapsulation.
- should reduce or avoid enzyme degradation and increase insulin permeability across the intestinal membrane.
- the permeability of the mucosal epithelium to enhance the absorption of insulin and provide the intact insulin to the blood circulation.
- must be safe after oral administration.

- Insulin should be available for interaction with cell surface receptors and captured by lymphatic cells, or pass through or be entrapped in the lymph nodes or transferred to the systemic circulation, provided that the particles remain as such and particle size within acceptable limit.

**DIVERSE CARRIERS USED FOR NON INVASIVE DRUG DELIVERY OF INSULIN**

**Insulin-loaded Bioadhesive PLGA Nanoparticles for Oral Drug Delivery**

PEGylation play an important role in increasing the stability of several therapeutic proteins. For the drug delivery system of proteins and peptides Poly (D, L-lactide-co-glycolide) nanoparticles (PLGA-NP) have been used extensively. Chitosan PLGA nanoparticle has some attractive properties, such as a mucosal adhesion, positive charge, and absorption enhancement, which increase the duration of residence of insulin in *in-vitro* and improve its bioavailability in *in-vivo* for oral delivery. The negative surface charge present on PLGA nanoparticles tends to reduce the oral bioavailability by limiting the diffusion of insulin nanoparticles across the mucus layer. Cationic chitosan can be used to coat and modify the surface charge of PLGA nanoparticles.

**Polymeric Hydrogels for Oral Insulin Delivery**

Nature of the polymer might enhance the residence time of a drug delivery system inside the GI tract.Polymerichydrogels protect insulin from enzymatic degradation in acidic environment of stomach and delivers insulin effectively in the intestinal region. Swelling and de-swelling mechanisms of the hydrogel under different pH conditions of the body control the release of insulin. A Combination of enzyme inhibitors and polymeric systems has potential to increase the potency of orally given insulin.

**Acrylic Polymers for Oral Insulin Delivery**

Acrylic polymers are synthetic mucoadhesive polymers, basically intended for oral drug delivery. Various techniques used to generate synthetic polymers are nano precipitation, solvent evaporation, freeze-drying, spray drying of emulsions and supercritical fluid technology. Methacrylic acid or acrylic acid are used as copolymer because of their pH-sensitive nature and ability to bind calcium, and poly (ethylene glycol) because of its ability to stabilize and protect proteins.

**Aerosolized Liposomes for Pulmonary Delivery of Insulin**

Pulmonary route for systemic delivery of peptides and proteins is paid more attention because it’s a non-invasive method of administrating insulin and it is valuable for the delivery of large molecular proteins. This method is effective for both type 1(T1DM) and type 2 diabetes mellitus (T2DM). Generally lungs have large surface area (approximate about 100 square metres) and acts as an ideal target for insulin delivery.

**Chitosan–zinc–insulin Complex**

Chitosan, a biodegradable polymer and a cationic polysaccharide, has been extensively known for the preparation of nanoparticles for oral controlled...
delivery. Derivatization of Chitosan polymers afford improvement in drug retention capability, provide improved permeation, enhanced mucoadhesion and sustained release of therapeutic agents.

MARKET STATUS OF ORAL INSULIN FORMULATIONS
In the recent years, the oral dosage of insulin is at different stages of developments from pre-clinical testing to Phase II clinical trials. Oral in has been successfully tried in Type 1 and Type 2 diabetic patients and when the results were compare with subcutaneous injection it was find appropriate for controlling blood glucose level. A remarkable progress has been reported in the recent past years for the delivery of insulin by non-invasive routes. Some of other hormonal drugs, such as calcitonin and vasopressin, are available in the form of intranasal sprays. The field of oral insulin delivery took an enormous step ahead with the approval of Exubera® from Pfizer and Nektar Therapeutics (Table 1).

CONCLUSION
An extensive number of people especially in developed countries suffered from diabetes. The pharmacotherapy for T1DM and T2DM treatment is subcutaneous injection of insulin. Discomfort, pain and local infection are the main reasons for patient non-compliance. On the other hand, the development of oral dosage form of insulin formulation can improve patient acceptability. Painful administration and phobia from invasive routes have encouraged scientists to research new possible methods for oral insulin delivery. Various barriers to insulin uptake by oral routes have its own set of advantages and disadvantages. Over the last few years, researchers have focused on oral insulin delivery. Although extensive human clinical studies are still the major requirement of oral insulin drug delivery and for the optimisation of physiochemical and pharmacokinetic parameters of insulin in drug carriers for diabetes treatment.

REFERENCES
Figure 1: Various challenges to oral insulin drug delivery

Table 1: List of clinically tested oral insulin formulation

<table>
<thead>
<tr>
<th>Company</th>
<th>Name</th>
<th>Product</th>
<th>Development phase</th>
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<tr>
<td>Biocon/Bristol-Myers Squibb Access Pharmaceuticals, Inc</td>
<td>IN-105 CobOral™</td>
<td>Conjugate Insulin</td>
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<td>Aphios Corporation</td>
<td>APH-0907</td>
<td>Insulin coated insulin-loaded nanoparticles</td>
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<tr>
<td>Diabetology Ltd</td>
<td>Capsulin™ OAD</td>
<td>Insulin with delivery system Axxcess™</td>
<td>II</td>
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<tr>
<td>Diasome Pharmaceuticals, Inc. Emisphere Technologies, Inc.</td>
<td>HDV-Insulin Eligen® insulin</td>
<td>Hepatic-directed vesicle-insulin (nanocarrier) (Eligen®)</td>
<td>III</td>
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<tr>
<td>Jordanian Pharmaceutical Manufacturing Co. PLC</td>
<td>JPM oral</td>
<td>Liquid delivery system with insulin-chitosan nanoparticles (GIPET®)</td>
<td>I</td>
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<td>Novo Nordisk A/S</td>
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<td>Insulin analog with an oral delivery system</td>
<td>I</td>
</tr>
<tr>
<td>Oramed, Inc.</td>
<td>ORMD-0801</td>
<td>Insulin with protein oral delivery system</td>
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<td>Oshadi Drug Administration Ltd</td>
<td>Oshadi Icp.</td>
<td>Insulin, proinsulin, and C-peptide in Oshadi carrier</td>
<td>II</td>
</tr>
<tr>
<td>NOD Pharmaceuticals, Inc./ Shanghai Biolaxy, Inc.</td>
<td>Nodlin</td>
<td>Insulin with bioadhesive nanoencapsulation (NOD Tech)</td>
<td>II</td>
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<tr>
<td>Transgene Biotek Ltd.</td>
<td>TBL1002OI</td>
<td>Proprietary nanotechnology Trabi-Oral™</td>
<td>Preclinical</td>
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