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REVIEW ARTICLE

ORAL DRUG DELIVERY OF INSULIN IN DIABETES MELLITUS: AN ATTRACTIVE ALTERNATE TO OVERCOME INVASIVE ROUTE

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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[1]. 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[2]. Oral bioavailability of insulin is below 1% so there is a big challenge to improve it up to 30–50%[3]. 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 eviction 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[4,5].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[5]. In order to attain an ideal oral peptide drug delivery system, some alternates will be required to encapsulate the insulin[6]. 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[7]. 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 nano particles, lipid nano particles and PEGylated calcium phosphate nanoparticles etc as oral drug delivery carriers for insulin[8].

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 Daare 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[9]. 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[10].

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, α-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[9]. Insulin can be available for absorption through GIT when the enzymatic attack is either diminished or overcome[11]. Although Insulin is not subject to proteolytic breakdown by brush border enzymes[12].

Poor Intestinal transport of insulin

The anatomy of insulin is very exquisite. Insulin is susceptible to oxidative damage when it react with amino acids[9]. In other words we can say that insulin has low permeability via intestinal mucosa[11].

Dosage form stability

Proteins changesits 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 calorimetery, light scattering, electrophoresis, and gel filtration[12] (Figure 1).

Features of an absoluteoral 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[13].

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[14].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[15]. 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[16].

Polymeric Hydrogels for oral insulin delivery

Nature of the polymer might enhance the residence time of a drug delivery system inside the GI tract[17]. 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[15].

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[15]. 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[18].

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[14]. This method is effective for both type 1(T1DM) and type 2 diabetes mellitus (T2DM)[19]. Generally lungs have large surface area (approximate about 100 square metres) and acts as an ideal target for insulin delivery[20].

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[8].

Table 1: List of clinically tested oral insulin formulation.

Company	Name	Product	Development phase
Biocon/Bristol-Myers Squibb	IN-105	Conjugate Insulin	II
Access Pharmaceuticals, Inc	CobOral™	Insulin coated insulin-loaded nanoparticles	II
Aphios Corporation	APH-0907	Nanoencapsulated insulin/ biodegradable polymer nanospheres	Preclinical
Diabetology Ltd	Capsulin™ OAD	Insulin with delivery system Axcess™	II
Diasome Pharmaceuticals, Inc.	HDV-Insulin	Hepatic-directed vesicle-insulin (nanocarrier)	III
Emisphere Technologies, Inc.	Eligen® insulin	Insulin with chemical delivery agents (Eligen®)	I
Jordanian Pharmaceutical Manufacturing Co. PLC	JPM oral	Liquid delivery system with insulin-chitosan nanoparticles	I
Novo Nordisk A/S	NN1952	Insulin analog with an oral delivery system GIPET®	
Oramed, Inc.	ORMD-0801	Insulin with protein oral delivery system POD™	II
Oshadi Drug Administration Ltd	Oshadi Icp.	Insulin, proinsulin, and C-peptide in Oshadi carrier	II
NOD Pharmaceuticals, Inc./ Shanghai Biolaxy, Inc.	Nodlin	Insulin with bioadhesive nanoencapsulation (NOD Tech)	II
Transgene Biotek Ltd.	TBL1002OI	Proprietary nanotechnology Trabi-Oral™	Preclinical

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[21]. 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[22]. 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[5] (Table 1).

CONCLUSIONS

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.

AUTHOR'S CONTRIBUTION

Mathur P: writing original draft, methodology, investigation, formal analysis, conceptualization. **Mathur CK:** writing, review and editing, methodology, formal analysis, conceptualization. **Mathur K:** writing, review, and editing, methodology. The final manuscript was read and approved by all authors.

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DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Mariko Morishita, Isao Morishita, Kozo Takayama, Yoshiharu Machida, Tsuneji Nagai. Novel oral microsphere of insulin with protease inhibitor protecting from enzymatic degradation. Int J Pharmaceutics 1992; 78: 1-7. *https://doi.org/10.1016/0378-5173(92)90348-6*
2. Mariko Morishita, Nicholas A. Peppas. Is the oral route possible for peptide and protein drug delivery? Drug Discov Today 2006: 11: 905-907. *https://doi.org/10.1016/j.drudis.2006.08.005*
3. Verma A, Kumar N, Malviya R, Sharma PK. Emerging trends in noninvasive insulin delivery. J Pharmaceutics. 2014: 1-9. *https://doi.org/10.1155/2014/378048*
4. Sonia TA, Chandra P. Sharma. An overview of natural polymers for oral insulin delivery. Drug Discov Today 2012: 17: No.13/14: 785-792. *https://doi.org/10.1016/j.drudis.2012.03.019*
5. El-Sayed Khafagy, Mariko Morishita , Yoshinori Onuki, Kozo Takayama. Current challenges in non-invasive insulin delivery systems: a comparative review. Adv Drug Deliv Rev 2007: 59: 1521–1546. *https://doi.org/10.1016/j.addr.2007.08.019*
6. Chun Y. Wong, Hani Al-Salami, Crispin R. Dass. Microparticles- microcapsules and microspheres: a review of recent developments and prospects for oral delivery of insulin. Int J Pharmaceutics 2017; 537(1-2): 223-244.

https://doi.org/10.1016/j.ijpharm.2017.12.036
7. Wenji Deng, Qian Xie, Huan Wang, Zhiguo Ma, Baojian Wu, Xingwang Zhang. Selenium nanoparticles as versatile carriers for oral delivery of insulin. Nanomed: Nanotech, Biol Med 2017; 13(6):1965-1974. *https://doi.org/10.1016/j.nano.2017.05.002*
8. Subhashini Yaturu. Insulin therapies: Current and future trends at dawn. World J Diabetes 2013:4(1): 1-7. *https://doi.org/10.4239/wjd.v4.i1.1*
9. Rajashree S. Hirlekar, Esha J. Patil, Srinivas R. Bhairy.Oral Insulin Delivery: Novel strategies. Asian J Pharmaceutics 2017: 11 (3): 434-443. *https://doi.org/10.22377/ajp.v11i03.1443*
10. Behera A, Biswal S, Kumar SS. Nanomedicine and type 2 diabetes: A review. J Pharm Res 2018; 12(3): 370-377. *https://doi.org/10.1038/nrd4477*
11. Kinesh VP, Neelam DP, Punit BP, Bhavesh SV, Pragna KS. Novel approaches for oral delivery of insulin and current status of oral insulin products. Intl J Pharm Sci Nanotech 2010; 3(3):1057-1064.
12. Varshney HM, Kumar R, Mohan S. Novel approaches for insulin delivery: Current status. Int J Therap App 2012: 7: 25-31.
13. Thundiparambil AS, Sharma PC. Oral Delivery of Insulin; Woodhead Publishing Series in Biomedicine: Number 41: 2014: 258. *https://doi.org/10.1016/C2013-0-18177-9*
14. Kenneth D. Hinds *et al.* PEGylated insulin in PLGA microparticles. *In vivo* and *in vitro* analysis. J Cont Rel 2005; 104:447–460. *https://doi.org/10.1016/j.jconrel.2005.02.020*
15. Yasmeen T, Mamatha, Zubair M, Begum S, Tayyaba M. Various emerging trends in insulin drug delivery systems. British J Pharm Res 2015: 5(5): 294-308. *https://doi.org/10.9734/BJPR/2015/12528*
16. Chun Y. Wong, Hani Al-Salami, Crispin R. Dass. Potential of insulin nanoparticle formulations for oral delivery and diabetes treatment. J Cont Rel 2017; 264:247-275. *https://doi.org/10.1016/j.jconrel.2017.09.003*
17. Furtado S, Danielle A, Roxanne B, Olivier G, Celinda G, Bubbers E, Mathiowitz NE. Oral delivery of insulin loaded poly (fumaric-co-sebacic) anhydride microspheres. Int J Pharmaceutics 2008: 347:149–155. *https://doi.org/10.1016/j.ijpharm.2007.06.039*
18. Aaron C. Foss, Takahiro G, Mariko M, Nicholas A. Peppas. Development of acrylic-based copolymers for oral insulin delivery. European J Pharmaceutics Biopharm 2004:57: 163–169. *https://doi.org/10.1016/S0939-6411(03)00145-0*
19. George S, Roy A. Novel approaches in insulin drug delivery – a review. Int J Drug Dev Res 2013: 5 (4): 1-5. *https://doi.org/10.2174/1389450119666180523092100*
20. S. Bala Murali Mohan, Deepthi.B 1, Gourineny Bhanusree. Review of recent trends in non-invasive insulin therapy for diabetes mellitus. World J Pharmacy Pharm Sci 2017: 3(8): 1870-1884. *https://doi.org/10.5001/omj.2012.68*
21. Kamlesh J Wadher, Kalsait R, Umekar M. Oral insulin delivery: facts, developments and challenges, Scholars Research Library; Der Pharmacia Lettre 2009; 1 (2): 121-129. *https://doi.org/10.1073/pnas.1722338115*
22. Christiane Damge, Catarina Pinto Reis, Philippe Maincent. Nanoparticle strategies for the oral delivery of insulin. Expert Opin. Drug Deliv 2008; 5(1):45-68. *https://doi.org/10.1517/17425247.5.1.45*