Asian Journal of Pharmaceutical Technology and Innovation

Review Article

Received on: 02-12-2013
Accepted on: 03-12-2013
Published on: 05-12-2013
Corresponding Author:

Prashant V. Shinde*

Contact no: 9890855002

*Email Id- prashantvs99@yahoo.com

Novel Carrier Systems For Oral Delivery Of Insulin

Prashant V. Shinde

ABSTRACT

The oral route is considered to be the most convenient and desired route of drug delivery, especially when repeated or routine administration is necessary 1. Insulin is usually administered to diabetic patients through subcutaneous injection. However, the problems encountered with subcutaneous insulin injections are pain, allergic reactions, hyperinsulinemia, and insulin lipodystrophy around the injection site 2. Insulin if administered via the oral route will help eliminate the pain caused by injection, psychological barriers associated with multiple daily injections such as needle anxiety 3 and possible infections 4. In addition, oral insulin is advantageous because it is delivered directly to the liver, its primary site of action, via the portal circulation, a mechanism very similar to endogenous insulin; subcutaneous insulin treatment however does not replicate the normal dynamics of endogenous insulin release, resulting in a failure to achieve a lasting glycemic control in patients 5, 6. In light of the above distinct benefits, pharmaceutical technologists have been trying to design an oral delivery system for insulin. Such is the interest in oral insulin delivery that some pharmaceutical companies are solely focused on it.

Key-words:

Oral insulin, carriers, nanoparticles, liposomes, microspheres.

Challenges to Oral Insulin Delivery:

Generally, peptides and proteins such as insulin cannot be administered via the oral route due to rapid enzymatic degradation in the stomach, inactivation and digestion by proteolytic enzymes in the intestinal lumen, and poor permeability across intestinal epithelium because of its high molecular weight and lack of lipophilicity, and dosage form stability [7, 8, 9]. The oral bioavailability of most peptides and proteins therefore is less than 1%. The challenge here is to improve the bioavailability to anywhere between 30 – 50%.[10]

Attempted Oral Insulin Delivery Systems:

Most peptides are not bioavailable from the GIT after oral administration [12]. Therefore, successful oral insulin delivery involves overcoming the enzymatic and physical barriers [11] and taking steps to conserve bioactivity during formulation processing [6]. In developing oral protein delivery systems with high bioavailability, three practical approaches might be most helpful: [13]

(1) Modification of physicochemical properties such as lipophilicity and enzyme susceptiblity.

(2) Addition of novel function to macromolecules.

(3) Use of improved carrier systems.

The various oral delivery systems which have been attempted to deliver insulin orally either singly or in a synergistic approach can be categorized as follows:

Enzyme Inhibitors: Insulin is degraded in the GIT by pepsin and other proteolytic enzymes. Enzyme inhibitors slow the rate of degradation of insulin which increases the amount of insulin available for absorption [6]. The earliest studies involving enzyme inhibitors were carried out with sodium cholate along with aprotinin which improved insulin absorption in rats [14]. Significant hypoglycemic effects were also obtained following large intestinal administration of insulin with camostat mesilate, bacitracin [15]. Other inhibitors which have shown promise are leupeptin [16], FK-448 [17], a potent and specific inhibitor of chymotrypsin and chicken and duck ovomucoid [18]. In one study, polymers cross-linked with azoaromatic groups formed an impervious film to protect insulin from digestion in the stomach and small intestine. Upon reaching the large intestine, the indigenous microflora degraded the polymer film, thereby releasing the drug into the lumen of the colon for absorption [19]. The use of enzyme inhibitors in long-term therapy however remains questionable because of possible absorption of unwanted proteins, disturbance of digestion of nutritive proteins and stimulation of protease secretion [20].

Penetration Enhancers: Another strategy for oral insulin delivery is to promote absorption through the intestinal epithelium by permeation enhancement. Hydrophilic molecules like insulin are adsorbed to the

apical membrane and are internalized by endocytosis [6]. Another theory suggests absorption via paracellular transport. Tight junctions between each of the cells in the epithelium prevent water and aqueous soluble compounds from moving past those cells. Hence, approaches for modulating tight-junction permeability to increase paracellular transport have been studied [21]. A number of absorption enhancers are available that cause these tight junctions to open transiently allowing water-soluble proteins to pass. Absorption may be enhanced when the product is formulated with acceptable safe excipients [22]. These include substances like bile salts, surfactants, trisodium citrates, chelating agents like EDTA [23], labrasol [24]. Insulin transport across Caco-2 cells was shown to be dramatically increased by conjugation of insulin with TAT, a cell penetrating peptide (CPP) [25]. The drawbacks with penetration enhancers include lack of specificity, i.e., they allow all content of the intestinal tracts including toxins and pathogens the same access to the systemic bloodstream [26], and risk to mucous membranes by surfactants and damage of cell membrane by chelators [2]. Mucoadhesive polymers have been proven to be safe and efficient intestinal permeation enhancers for the absorption of protein drugs [27, 28]. The zonula occludens toxin, chitosan, thiolated polymers, and Pz-peptide have all demonstrated capacity to increase macromolecular drug absorption [13].

Combinational strategies involving enzyme inhibitors and absorption enhancers have been effective in increasing bioavailability of insulin. Combinations like sodium cholate and soybean trypsin inhibitor [14], sodium lauryl sulphate and aprotinin [29] have resulted in reduction in blood glucose in dogs.

Carrier Systems:

The oral bioavailability of insulin can be enhanced by the use of novel carrier systems which deliver insulin to the target site of absorption [2]. Liposomes, microspheres and nanoparticles have been developed for use as carrier systems for insulin.

Liposomes: These are tiny spheres formed when phospholipids are combined with water [2].

Encapsulating insulin in liposomes results in enhanced oral absorption of insulin. However, the high doses of liposome-entrapped insulin required coupled with variability in glycemic response limits its use [30]. Other drawbacks include instability, leakage of entrapped drug, and low drug carrying capacity [2].

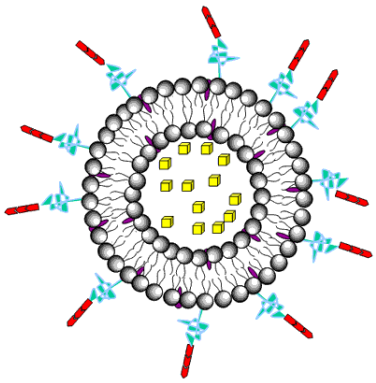


Figure 1: Liposomes

Encapsulation of insulin in liposomes

Microspheres: Insulin can be encapsulated in a microcapsule or dispersed in a polymer matrix. Microspheres are prepared by emulsification using natural (gelatin or albumin) or synthetic polymers (polylactic or polyglycolic acid) [2]. Morishita *et al* [31] used microspheres for insulin delivery in rats. Their study showed that L-microspheres carrying insulin and aprotinin enhanced insulin absorption. Insulin-loaded alginate microspheres complexed with cyclodextrins have an absorption enhancing effect leading to increase in bioavailability [32]. Qi and Ping [33] studied the oral coadministration of insulin enteric microspheres with sodium N-(8-2-hydroxybenzoyl amino) caprylate (SNAC). EDTA was administered before the insulin oil solution was given to rats. A decrease in glucose levels, which primarily resulted from EDTA's enzyme inhibiting properties was observed [34]. In a recent study, Eudragit S100 microspheres on oral administration protected insulin from proteolytic degradation in the GIT and produced hypoglycemic effect [9]. Microspheres encapsulated with chitosan phthalate polymer protect the insulin from enzymatic degradation with an insulin-loading capacity of 62% and may be a potential carrier for oral insulin delivery [35].

Nanoparticles:

Nanoparticles have been extensively studied as carriers for oral insulin delivery [36]. Polymeric nanoparticles (nanocapsules and nanospheres) are of special interest from a pharmaceutical point of view. The biological effect of insulin nanocapsules depends on the amount of both insulin and polymer. The nature of polymers strongly influences the nanoparticle size and release profile [26]. The intensity and duration also depends on the site of administration (65% ileum, 59% stomach, 52% duodenum and jejunum, 34% colon). The nanoparticles protect insulin against enzymatic degradation in vitro [37]. Synthetic polymers used for nanoparticle formulation include polyalklylcyanoacrylate [38], polymethacrylic acid [8], polylactic-co-glycolic acids (PLGA) [39].

Insulin encapsulation with Nanoparticles

Polymer	Size (nm)	Species	Observations	Ref
Chitosan- (γ-PGA)	110-115	Rat	Significant reduction of blood glucose level up to 10 hours	4
Lecithin-modified solid NP	300	Rat	Bioavailability of 4.46% and 4.49%	36
Poly(isobutylcyanoacrylate)	270-340	Rat	Decrease of glycemia from 300mg/dl to 125 mg/dl	38
Chitosan	270-340	Rat	Effective glycemic control at doses of 50 U/kg and 100 U/kg	40
Acrylic-based copolymer	200-2000	Rat	Significant reduction in serum glucose	41
Poly(ε-caprolactone)-Eudragit RS	358	Rat	Bioavailability of 13% over 24h with maximal effect at 100 U/kg	42
Soybean phosphatidylcholine (SPC)	200	Rat	Oral bioavailability of 7.7%	43
Chitosan	250-400	Rat	Pharmacological availability of 14.9%	45

Natural polymers used include chitosan [4], alginate, gelatin, albumin [26] and lectin [34]. Chitosan has been the proven to have good permeation enhancing abilities via the paracellular pathway [27]. A recent study showed that insulin-loaded nanoparticles shelled with chitosan could effectively reduce the blood glucose level in a diabetic rat model [4]. An exhaustive review of nanoparticles as a potential oral delivery system for proteins has been done by Rieux *et al* [26].

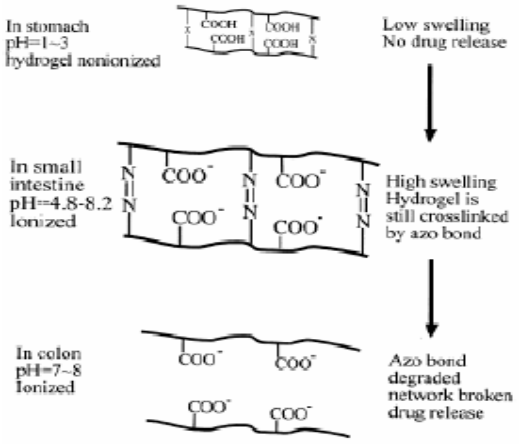
Chemical Modification: Modifying the chemical structure and thus increasing its stability is another approach to enhance bioavailability of insulin. An example of chemical modification is that of hexyl-insulin monoconjugate 2 (HIM-2) wherein a short chain polyethylene glycol (PEG) linked to an alkyl group is in turn linked to LYS-29 of the beta chain of insulin [22]. Alteration of the physicochemical characteristics leads to enhanced stability and resistance to intestinal degradation of oral insulin [44]. Shen *et al* [45] recently demonstrated improved efficacy of orally administered insulin by conjugating insulin with transferrin through disulfide linkages.

Bioadhesive Systems: Mucoadhesive delivery systems adhere to the mucous gel layer covering mucosal membranes. A high drug concentration is therefore present for absorption due to the intimate contact with the mucosa. As a result, numerous mucoadhesive delivery systems like chitosan [46], sodium salicylate, and polyoxyethylene-9-lauryl ether [47] have been proposed. The bioadhesive systems may however be affected by the mucous turnover of the GIT, which varies based on the site of absorption [2, 13, 28].

Emulsions: Cho and Flynn [12] developed water-in-oil microemulsions in which the aqueous phase is insulin and oil phase is lecithin, non-esterified fatty acids and cholesterol in critical proportions. Invivo

studies showed substantial reduction in blood glucose. Recent studies have focused on enteric-coated dry emulsion formulations prepared from solid-in-oil-in-water emulsions. These responded to changes in external environment suggesting potential application for oral insulin delivery.

Hydrogels: These are cross-linked networks of hydrophilic polymers, which are able to absorb large amounts of water and swell, while maintaining their three-dimensional structure [48]. Complexation hydrogels are suitable candidates for oral delivery of proteins and peptides due to their abilities to respond to changes in pH in the GI tract and provide protection to the drugs from the harsh environment of the GI tract [7].



Mechanism of Complexation Hydrogels [11]

Complexation hydrogels such as poly (methacrylic acid-g-ethylene glycol) P(MAA-g-EG) [7, 49], P(PAA-g-EG) have been used for this purpose. Tuesca *et al* [11] modified the network of the P(MAA-g-EG) hydrogel and combined it with a chemically modified insulin species in an attempt to improve bioavailability. Poly (ethylene glycol) dimethacrylates (PEGDMA) have been used as pH-sensitive hydrogels [50]. Oral administration of insulin entrapped in amidated pectin hydrogel beads in streptozotocin (STZ)-diabetic rats resulted in a concomitant reduction in plasma glucose concentration [51].

Developments in oral insulin delivery: The oral delivery of insulin has always been a significant challenge for pharmaceutical researchers. The development of oral insulin is at different stages for different companies and covers a broad spectrum from preclinical testing to Phase II clinical trials [52]. A notable advancement is the completion of phase II trials of oral insulin product, hexyl-insulin monoconjugate 2 (HIM 2) which has been found to be safe and well tolerated [53]. Human clinical trials with conjugated insulin are a clear demonstration that proteins can be developed into therapeutically viable products [22]. In October 2006, Emisphere announced preliminary results of Phase II trials of oral insulin product developed with Eligen™ technology. Emisphere's Eligen™ technology makes use of small

hydrophobic organic compounds that interact noncovalently with macromolecules, increasing their lipophilicity and enhancing absorption. Covalent and noncovalent drug modifications for increasing membrane permeability are currently employed by two companies, Nobex (now Biocon) and Emisphere Technologies. Clinical trials with type 1 and type 2 diabetic patients have demonstrated initial efficacy, but low bioavailability (estimated at 5%) continues to be a problem [13].

Conclusion:

The oral route for insulin delivery might be possible in the near future with the use of using superior materials as carriers for insulin delivery systems. However, only further research into delivery system*s* can make it possible for the oral route to represent a viable route of administration. Maximization of the absorptive cellular intestinal uptake and stabilization of insulin at all stages before it reaches its target will determine its final efficiency. The chances for a market launch will depend on several factors such as efficacy and safety as well as economic reasons. Although considerable efforts have been already made to deliver insulin orally, extensive and continuous comparison of in-vitro and in-vivo studies are essential to develop oral insulin delivery systems in the foreseeable future.

References:

1. Kim BY, Jeong JH, Park K, Kim JD. Bioadhesive interaction and hypoglycemic effect of insulin-loaded lectin-microparticle conjugates in oral insulin delivery system. J. Cont. Release 2005; 102:525-538.
2. Gowthamarajan K, Kulkarni GT. Oral Insulin – Fact or Fiction? Possibilities of achieving oral delivery for insulin. Resonance, May 2003, 38-46.
3. Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int. J. Obesity 2002; 26, Suppl 3, S18 – S24.
4. Lin YH, Mi FL, Chen CT et al. Preparation and characterization of nanoparticles shelled with chitosan for oral insulin delivery. Biomacromolecules 2007; 8:146-152.
5. Morishita M, Goto T, Nakamura K, Lowman AM, Takayama K, Peppas NA. Novel oral insulin delivery systems based on complexation polymer hydrogels: Single and multiple administration studies in type 1 and 2 diabetic rats. J. Cont. Release 2006; 110:587-594.
6. Agarwal V, Khan MA. Current status of the oral delivery of insulin. Pharmaceutical Technology, October 2001, 76-90.
7. Nakamura K, Murray RJ, Joseph JI, Peppas NA, Morishita M, Lowman AM. Oral insulin delivery using P(MAA-g-EG) hydrogels: effects of network morphology on insulin delivery characteristics. J. Cont. Release 2004, 95:589-599.
8. Sajeesh S, Sharma CP. Cyclodextrin-insulin complex encapsulated polymethacrylic acid based nanoparticles for oral insulin delivery. Int. J. Pharm. 2006 (In Press).
9. Jain D, Panda AK, Majumdar DK. Eudragit S100 entrapped insulin microspheres for oral delivery. AAPS PharmSciTech 2005, 1-27.
10. Lee VH. "Oral route of peptide and protein drug delivery", Peptide and Protein Drug Delivery, Chapter 16, Marcel Dekker Inc. 1991, 691–738.
11. Tuesca A, Lowman A. The oral delivery of insulin using protein conjugates in complexation hydrogels. Poster presentation, Biomaterials and Drug Delivery Laboratory 2006, Drexel University.
12. Cho YW, Flynn M. Oral delivery of insulin. Lancet 1989; 1518-1519.
13. Morishita M, Peppas NA. Is the oral route possible for peptide and protein drug delivery? Drug Discovery Today, October 2006, Vol. 11, Num. 19/20.
14. Ziv E, Lior O, Kidron M. Absorption of protein via the intestinal walls: A quantitative model. Biochem. Pharmacol. 1987; 39 (7), 1035–1039.
15. Yamamoto A, Taniguchi T, Rikyuu K et al. Effects of various protease inhibitors on the intestinal absorption and degradation of insulin in rats. Pharm. Res. 1994; 11 (10), 1496–1500.
16. Liu H, Tang R, Pan WS, Zhang Y, Liu H. Potential utility of various protease inhibitors for improving the intestinal absorption of insulin in rats. J Pharm Pharmacol. Nov 2003;55(11):1523-9.
17. Fujii S, Yokoyama T, Ikegaya K, Sato F, Yokoo N. Promoting effect of the new chymotrypsin inhibitor fk-448 on the intestinal absorption of insulin in rats and dogs. J. Pharm. Pharmacol. 1985; 37 (8), 545–549.
18. Agarwal V, Reddy IK, Khan MA. Polyethylacrylate-based microparticulate of insulin for oral delivery: preparation and in vitro dissolution stability in the presence of enzyme inhibitors. Int. J Pharm. 2001; 225 (1–2), 31–39.
19. Saffran M, Kumar GS, Savariar C, Burnham JC, Williams F, Neckers DC. A new approach to the oral administration of insulin and other peptide drugs. Science 1986 Sep 5; 233(4768):1081-4.
20. Shah RB, Ahsan F, Khan MA. Oral delivery of proteins: Progress and prognostication. Crit. Rev. Ther. Drug Carrier Syst. 2002, 19(2): 135–169.
21. Salamat-Miller N, Johnston TP. Current strategies used to enhance the paracellular transport of therapeutic polypeptides across the intestinal epithelium. Int. J. Pharm. 2005; 294: 201–216
22. Soltero R, Ekwuribe N. The oral delivery of protein and peptide drugs- A report; Innovat. Pharmaceut. Technol. 2001, 1:106–110.
23. Li CL, Deng YJ. Oil-based formulations for oral delivery of insulin. J. Pharm. Pharmacol. 2004; 56 (9), 1101–1107.
24. Eaimtrakarn S, Ramaprasad YV, Ohno T et al. Absorption-enhancing effect of labrasol on the intestinal absorption of insulin in rats, J. Drug Target. 2002; 10 (3), 255–260.
25. Liang JF, Yang VC. Insulin-cell penetrating peptide hybrids with improved intestinal absorption efficiency. Biochem. Biophys. Res.Commun. 2005; 335: 734–738.
26. Rieux A, Fievez V, Garinot M, Schneider YJ, Preat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. J. Cont. Release 2006; 116: 1-27.
27. Thanou M, Verhoef JC, Junginger HE. Chitosan and its derivatives as intestinal absorption enhancers. Adv. Drug. Delivery. Rev 2001, 50: S91-S101.
28. Plate NA, Valuev IL, Sytov GA. Mucoadhesive polymers with immobilized proteinase inhibitors for oral administration of protein drugs. Biomaterials 2002; 23 (7), 1673–1677.

29. Kraeling MEK, Ritschel WA. Development of a colonic release capsule dosage form and the absorption of insulin. Meth. Find. Exp. Clin. Pharmacol. 1992; 14 (3): 199–209.
30. Spangler RS. Insulin administration via liposomes. Diabetes Care, Vol 13, Issue 9 911-922.
31. Morishita M, Takayama K, Machida Y, Nagai T. Enteral insulin delivery by microspheres in three different formulations using Eudragit L-100 and S-100. Int. J. Pharm. 1993; 91: 29–37.
32. Timmy SA, Victor SP, Sharma CP, Kumari VJ. Betacyclodextrin complexed insulin loaded alginate microspheres – Oral delivery system. Trends Biomater. Artif. Organs. 2002 Vol 15(2): 48-53.
33. Qi R, Ping QN. Gastrointestinal absorption enhancement of insulin by administration of enteric microspheres and SNAC to rats. J. Microencapsul. 2004; 21 (1): 37–45.
34. Ghilzai NM. Oral insulin delivery in 2003. Business Briefings, Pharmagenerics 2003.
35. Ubaidulla U, Sultana Y, Ahmed FJ, Khar RK, Panda AK. Chitosan Phthalate Microspheres for Oral Delivery of Insulin: Preparation, Characterization, and In Vitro Evaluation. Drug Delivery January 2007, Vol. 14, No. 1.
36. Zhang N, Ping Q, Huang G, Xu W, Cheng Y, Han X. Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin. Int. J. Pharm 2006; 327: 153-159.
37. Michel C, Apahamian M, Defontaine L, Couvreur P, Damge C. The effect of site of administration in the gastrointestinal tract on the absorption of insulin from nanocapsules in diabetic rats. J. Pharmacy Pharmacol 1991, 43:1-5.
38. Damge C, Michel C, Aprahamian M, Couvreur P. New approach for oral administration of insulin with polyalkylcyanoacrylate nanocapsules as drug carrier. Diabetes 1988; 37: 246–251.
39. Carino GP, Jacob JS, Mathiowitz E. Nanosphere based oral insulin delivery. J. Cont. Release. 2000 Mar 1, 65(1-2):261-9.
40. Ma Z, Lim TM. Pharmacological activity of peroral chitosan-insulin nanoparticles in diabetic rats. Int. J. Pharm. 2005; 293: 271-80
41. Foss AC, Goto T, Morishita M, Peppas NA. Development of acrylic-based copolymers for oral insulin delivery. Eur. J. Pharm. Biopharm. 2004; 57:163–169
42. Damge C, Maincent P, Ubrich N. Oral delivery of insulin associated to polymeric nanoparticles in diabetic rats. J. Cont. Release 2007; 117:163-170
43. Cui F, Shi K, Zhang L, Tao A, Kawashima Y. Biodegradable nanoparticles loaded with insulin- phospholipid complex for oral delivery: Preparation, in vitro characterization and in vivo evaluation. J. Cont. Release 2006; 114:242-250
44. Patni P, Varghese D, Balekar N. Needle-free insulin drug delivery. Ind. J. Pharm. Sci, Jan-Feb 2006, 68(1): 1-132, 7-12.
45. Xia CQ, Wang J, Shen WC. Hypoglycemic effect of insulin-transferrin conjugate in streptozotocin-induced diabetic rats. J. Pharmacol. Exp. Ther. 2000; 295:594-600.
46. Pan Y, Li YJ, Zhao HY et al. Bioadhesive polysaccharide in protein delivery system: Chitosan nanoparticles improve the intestinal absorption of insulin in vivo. Int. J. Pharm.2002; 249:139-47
47. Hosny EA, al-Shora HI, Elmazar M.M. Effect of bioadhesive polymers, sodium salicylate, polyoxyethylene-9-lauryl ether, and method of preparation on the relative hypoglycemic produced by insulin enteric-coated capsules in diabetic beagle dogs. Drug Dev. Ind. Pharm. 2002; 28 (5):563–570.
48. Yupeng R, Seng LT. Oral GIT – Hydrogel system for treating type 1 diabetes – A Report.
49. Lowman AM, Morishita M, Kajita M, Nagai T, Peppas NA. Oral Delivery of Insulin Using pH-Responsive Complexation Gels. J. Pharm. Sci. 1999; 88 (9): 933-936
50. Kumar A, Lahiri SS, Singh H. Development of PEGDMA: MAA based hydrogel microparticles for oral insulin delivery. Int. J. Pharm. 2006 Oct 12; 323(1-2):117-24.
51. Musabayane CT, Munjeri O, Bwititi P, Osim EE. Orally administered, insulin-loaded amidated pectin hydrogel beads sustain plasma concentrations of insulin in streptozotocin-diabetic rats. J. Endocrinology 2000; 164:1–6.
52. Werle M. Innovations in oral peptide delivery – A report. Future Drug Delivery 2006.
53. Kipnes M, Still JG, Dandona P, Kosutic G, Tripathy D. Control of postprandial plasma glucose by an oral insulin product (HIM 2) in patients with type 2 diabetes. Diabetes Care 2003, 26:421– 426.