WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 3, 1471-1479. Review Article ISSN 2277– 7105

A REVIEW ON ALTERNATIVE ROUTES FOR INSULIN ADMINISTRATION

Ch. Amulya*, Dr. M. Eswar Gupta and Dr. I. Sudheer Babu

Sir C. R. Reddy College of Pharmaceutical Sciences, Shanthi Nagar, Eluru, A.P., India.

Article Received on
20 Jan. 2019,

Revised on 11 Feb. 2019,
Accepted on 01 March 2019

DOI: 10.20959/wjpr20193-14432

***Corresponding Author**
Ch. Amulya
Sir C. R. Reddy College of Pharmaceutical Sciences, Shanthi Nagar, Eluru, A.P., India.

ABSTRACT

Many routes were tried to administer insulin into the body. Intramuscular, intravenous and subcutaneous routes were first tried. Among them, subcutaneous and intravenous routes are commonly used routes of administering insulin. These routes need injectible methods to deliver insulin which causes lot of pain and discomfort to the patient. To make insulin delivery in an easier and simpler way and to increase comfort in patients, other routes of administration were also tried. These include oral, buccal, sublingual, rectal, transdermal, ocular, intrapulmonary, and intranasal routes. This article gives a bird's eye view of research carried out till date to administer insulin in a convenient route other than injectible route.

KEYWORDS: Insulin, Diabetes, Intra pulmonary route, Intra nasal route.

INTRODUCTION

Diabetes is a serious, chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Globally, an estimated 422 million adults are living with diabetes mellitus, according to 2016 data from the World Health Organization (WHO). The number of diabetes patients is likely to rise to 101 million in India by 2030, estimates the World Health Organisation (WHO). Insulin is a hypoglycaemic agent and was discovered by Banting and Best in 1921.[1] This hormone is very effective in treating diabetes mellitus. Insulin effectively lowers blood sugar in patients with type 1 and 2 diabetes. Many routes were tried to administer insulin into the body. Intramuscular, intravenous and subcutaneous routes were first tried. Among them, subcutaneous and intravenous routes are commonly used routes of administering insulin.

These routes need injectible methods to deliver insulin which causes lot of pain and discomfort to the patient.

To make insulin delivery in an easier and simpler way and to increase comfort in patients, other routes of administration were also tried. These include oral, buccal, sublingual, rectal, transdermal, ocular, intrapulmonary, and intranasal routes.

In the present article, some of the physiological basis, advantages and disadvantages of alternate routes of insulin administration are discussed.

Oral insulin: Many attempts were made to develop an oral insulin product, but none of them were successful. Researchers reported that insulin had very low oral bioavailability. The reasons for low bioavailability are, low gastro intestinal permeability of the large insulin molecule, lack of lipophillicity and rapid degradation of insulin by gastrointestinal enzymes.[2] Research is being done to encapsulate insulin to prevent its gastro intestinal degradation. In addition, some companies are using permeability enhancers to enhance the trans-epithelial transport of insulin in GIT.[3,4,5]

Buccal insulin: Buccal administration is a topical route of administration, insulin product is held in the buccal pouch. In recent years, buccal mucosa has emerged as a favourable site for insulin delivery as buccal mucosa offers rich vasculature, relatively immobile mucosa and an expanse of smooth muscle.[6] Insulin diffuses through the oral mucosa and enters directly into the blood stream. Buccal route of insulin has an advantage over oral insulin in that it bypasses the gastro intestinal degradation.[7]

Generex a Canadian - and U.S.-based Company developed Oral-lyn, buccal insulin for prandial insulin therapy.[3] This preparation is the only marketed buccal insulin formulation till date. It is a proprietary liquid formulation of human regular insulin that delivers insulin directly to the buccal mucosa utilizing the rapid mist technology.[8] This system allows fast access of the drug into systemic circulation but it showed low bio availability.[9] A larger dose of insulin needs to be applied for achieving therapeutic concentration for desired results.

Sublingual insulin: In this route, the product is placed under the tongue. The sublingual absorption of insulin has been increased by use of appropriate permeation enhancers.[10][11][12] The East Gate Biotech developed EGP-1214, a compressed tablet containing human recombinant insulin and designed for sublingual administration. Initial experiments of EGP-

1214 demonstrated that the developed sublingual insulin tablet is easy and convenient to use.[13] It does not irritate the sublingual mucosa and has a fast and reproducible onset of glucose lowering action (within 30 minutes). Further studies have to be carried out on this product to establish proper pharmacokinetic data.[13] Sublingual insulin tablet can become a product of choice for diabetic patients.

Rectal insulin: Rectal gels[14] and suppositories[15] for insulin delivery were prepared and they gave good results. Direct insulin absorption through buccal, sublingual, oral, rectal, and intra muscular routes without an absorption promoter has demonstrated that rectal absorption is more efficacious than any of the other routes.[16] The only disadvantage is, this route is practically difficult. Till now there is no insulin marketed product for rectal route.

Transdermal insulin: The large surface area of the skin makes it a convenient route for insulin delivery,[17] but the main problem is inefficient delivery of insulin through skin. The outer most layer of the skin, stratum corneum restricts the absorption of insulin. Many methods like Iontophoresis,[18] Sonophereis,[19] electroporation,[20] micro dermal abrasion[21] have been developed to increase the absorption of insulin Trans dermally. A device named Insupatch™, was developed which is supplied along with transdermal insulin pump. This pump increases the absorption of insulin by applying local heat to the skin.[22][23] These techniques cause skin injury, significant pain and discomfort in patients. Research works has to be carried out to prove the long term safety and usefulness of this route of administration.

Ocular delivery of insulin: Systemic absorption of insulin through ocular route has been reported to be effective using absorption enhancers.[24] A Gelfoam ® based eye device has been tested to prolong insulin delivery through eye.[25] This device needs to be inserted to the lower conjunctival sac which is not so convenient. Till now, no human trial has been reported with this route and an animal study failed to achieve significant plasma insulin concentration.[26]

Pulmonary route delivery of insulin: Many Devices have been developed for delivering insulin to the alveolar space and are examined clinically. The bioavailability of inhaled insulin for each of the devices varies.[27] An ideal device should deliver insulin in an appropriate manner to achieve optimal glycemic control. It should also be convenient for patients. Devices are usually nebulizers that are metered-dose inhalers or drug-powder

inhalers.[28] Currently dry-powder inhalers are most commonly used devices to deliver pulmonary insulin.[29]

The distal lung has a large surface area (145 m^2) with a thin (0.2 μM) alveolar epithelium for absorption of insulin.[31] The various factors which influence the distribution of insulin to the distal lung include size, shape, density, charge, particle speed, and ventilator parameters. In order for particles to be deposited in the alveolar space, their size should be between 1 and 3 μM; smaller particles are exhaled and particles >5 μM are deposited in the upper airways or swallowed.[32] Patient cooperation and appropriate ventilator technique are important to ensure proper delivery of drug to the deep lung.[33][34]

Nektar Therapeutics developed EXUBERA, the first inhaled insulin product which is marketed by Pfizer in 2006.[35] Launching of EXUBERA (EXU), to the market raised hopes that inhaled insulin would pave the way for other alternative routes of insulin administration (ARIA), i.e. oral insulin, nasal insulin or transdermal insulin. EXU was withdrawn from the market as it did not gain sufficient market success. Poor sales led Pfizer to withdraw it in 2007.[36] There after many other attempts to develop inhaled insulin were ended.

AFREZZA, a monomeric inhaled insulin developed by Mannkind, was approved by the FDA in 2014. It is new, quicker acting inhalable insulin with a different and safer pharmacokinetic profile in comparison to previously failed inhaled insulin.[37] AFREZZA uses techno sphere technology. In June, 2014, the FDA approved AFFREZA for both Type I and Type II adult diabetics, with a label restriction for patients having asthma, active lung cancer or Chronic Obstructive Pulmonary Disease (COPD).[38]

Techno sphere technology contains recombinant human insulin dissolved with powder fumaryl diketopiperazine.[39] Once inhaled, technosphere insulin is rapidly absorbed upon contact with lung surface.[40] It is delivered with a thumb size inhaler. Both components, insulin and powder (fumaryl diketopiperazine) are almost completely cleared from the lungs of healthy individuals within 12 hours of inhalation. In contrast to Exubera (8-9%) only 0.3% of insulin of inhaled insulin remained in lungs after 12 hours. Inhaled insulin successfully ruled out subcutaneous insulin resistance syndrome (a rare condition due to rapid degradation of insulin in subcutaneous tissue).

Intranasal Route: Much interest is given to intranasal insulin administration because nasal region has more complex plexus of small blood vessels which increases the absorption of drug. The surface area for intranasal insulin inhalation is much smaller (~180 cm^2) than intrapulmonary insulin but still intranasal insulin administration is more suitable for drug administration because of the characteristics of the upper airways.[41]

The factors effecting delivery of intranasal insulin include nasal mucus concentration, character of the nasal mucus,[42] speed of mucociliary clearance, character and thickness of the mucociliary membrane, nasal mucus enzymes. The bacteria present in the nose may also affect the absorption of insulin. One of the key factors for successful development of an intranasal insulin formulation is an absorption enhancer[43] that would deliver insulin efficiently across nasal membranes without causing damage to mucosa. A protein transduction domain (PTD) derived from human translationally controlled tumor protein, was used as absorption enhancers. The newly designed formulations with PTD represented a useful platform for intranasal delivery of insulin and other biomolecules.[44]

Nasal delivery avoids the major action of liver metabolism, which is observed with the subcutaneous route administration. Many clinical studies proved that this route of insulin administration is successful in long-term control of plasma glucose.[45-50] Many absorption enhancers such as aminoboronic acid derivatives, amastatin, and enzyme inhibitors improved intra nasal absorption.[51] Inhibition of the action of proteolytic enzymes present in nasal mucus has increased absorption of insulin by intranasal route. Use of surfactants,[52] gelified insulin,[53] bio adhesive microspheres,[54] phospholipids,[43] chitosan nanoparticles[54] and other enhancers increased absorption of intra nasally delivered insulin. Intranasal insulin delivery has little toxic effects. It has been well tolerated without any long-term side effects.[55] In some cases increased cough, nasal irritation, inflammation was noticed. An immediate but not long-term hypertension has been reported with intranasal use.[56] Insulin resistance has also occurred after intranasal insulin administration as in case of all other methods of insulin administration.

CONCLUSION

Some patients are hesitant to introduce injections in their daily routine. Diabetic patients will readily accept an effective non-injectable insulin dosage form. The market success of the dosage form will depend on ease and convenience of administration, and its cost.

REFERENCES

1. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus. Can Med Assoc J., 1922; 12: 141–6.
2. Ehud Arbit, M.D. and Miriam Kidron, Ph.D. Oral Insulin: The Rationale for This Approach and Current Developments. J Diabetes Sci Technol, 2009 May; 3(3): 562–567.
3. Rima B. Shah,[1] Manhar Patel,[2] David M. Maahs, and Viral N. Shah. Insulin delivery methods: Past, present and future. Int J Pharm Investig, 2016 Jan-Mar; 6(1): 1–9.
4. Sakloetsakun D, Dünnhaupt S, Barthelmes J, Perera G, Bernkop-Schnürch A. Combining two technologies: Multifunctional polymers and self-nanoemulsifying drug delivery system (SNEDDS) for oral insulin administration. Int J Biol Macromol, 2013; 61: 363–72.
5. Maroni A, Zema L, Del Curto MD, Foppoli A, Gazzaniga A. Oral colon delivery of insulin with the aid of functional adjuvants. Adv Drug Deliv Rev., 2012; 64: 540–56.
6. Kumria R, Goomber G. Emerging trends in insulin delivery: Buccal route. J Diabetol, 2011; 2: 1–9.
7. Lutz Heinemann, Ph.D.[1] and Yves Jacques, Ph.D. Oral Insulin and Buccal Insulin: A Critical Reappraisal. J Diabetes Sci Technol, 2009 May; 3(3): 568–584.
8. Bernstein G. Delivery of insulin to the buccal mucosa utilizing the Rapid Mist system. Expert Opin Drug Deliv. 2008; 5(9): 1047–1055.
9. Modi P, Mihic M, Lewin A. The evolving role of insulin in the treatment of diabetes using a novel Rapidmist^{TM} system. Diabetes Metab Res Rev., 2002; 181: S38-S42.
10. Nilam H. Patil, Padma V. Devarajan. Enhanced insulin absorption from sublingual microemulsions: effect of permeation enhancers. Drug Delivery and Translational Research, December 2014; 4(5–6): 429–438.
11. Cui CY, Lu WL, Xiao L, et al. Sublingual delivery of insulin: effects of enhancers on the mucosal lipid fluidity and protein conformation, transport, and in-vivo hypoglycemic activity. Biol Pharmaceut Bull, 2005; 28: 2279–88.
12. Patil NH, Devarajan PV. Insulin-loaded alginic acid nanoparticles for sublingual delivery. Drug Deliv., 2016; 23(2): 429-36.
13. EGP-1214 - INTRAORAL (SUBLINGUAL) INSULIN TABLET BY EASTGATE BIOTECH.
14. Ritschel WA, Ritschel GB, Ritschel BE, Lücker PW. Rectal delivery system for insulin. Methods Find Exp Clin Pharmacol, 1988; 10: 645–56.

15. Yamasaki Y, Shichiri M, Kawamori R, Kikuchi M, Yagi T, Ara S, et al. The effectiveness of rectal administration of insulin suppository on normal and diabetic subjects. Diabetes Care, 1981; 4: 454–8.
16. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. Diabet Med., 2003; 20: 886–98.
17. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol, 2008; 26: 1261–8.
18. Kanikkannan N. Iontophoresis-based transdermal delivery systems. BioDrugs, 2002; 16: 339–47.
19. Rao R, Nanda S. Sonophoresis: Recent advancements and future trends. J Pharm Pharmacol, 2009; 61: 689–705.
20. Charoo NA, Rahman Z, Repka MA, Murthy SN. Electroporation: An avenue for transdermal drug delivery. Curr Drug Deliv., 2010; 7: 125–36.
21. Andrews S, Lee JW, Choi SO, Prausnitz MR. Transdermal insulin delivery using microdermabrasion. Pharm Res., 2011; 28: 2110–8.
22. Freckmann G, Pleus S, Haug C, Bitton G, Nagar R. Increasing local blood flow by warming the application site: Beneficial effects on postprandial glycemic excursions. J Diabetes Sci Technol, 2012; 6: 780–5. [PMC free article] [PubMed]
23. Freckmann G, Pleus S, Westhoff A, Krinelke LG, Buhr A, Jendrike N, et al. Clinical performance of a device that applies local heat to the insulin infusion site: A crossover study. J Diabetes Sci Technol, 2012; 6: 320–7.
24. Dennis Pillion, J D Bartlett, E Meezan, M Yang. Systemic absorption of insulin delivered topically to the rat eye. Investigative Ophthalmology & Visual Science, December 1991; 32(12): 3021-7.
25. Yung-Chi Lee , Samuel H Yalkowsky. Systemic absorption of insulin from a Gelfoam(R) ocular device. International Journal of Pharmaceutics, December 1999; 190(1): 35-40.
26. Morgan RV. Delivery of systemic regular insulin via the ocular route in cats. J Ocul Pharmacol Ther., 1995; 11: 565–73.
27. Patton JS, Bukar JG, Eldon MA. Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. Clin Pharmacokinet, 2004; 43(12): 781–801.
28. Remigius Uchenna Agu, Michael Ikechukwu Ugwoke, Michoel Armand, Renaat Kinget and Norbert Verbeke. The lung as a route for systemic delivery of therapeutic proteins and peptides. Respiratory Research 2001; 2: 198–209.
29. Garcia-Contreras L, Smyth H. Liquid-spray or dry powder systems for inhaled delivery of peptide and proteins? American Journal of Drug Delivery, 2005; 3: 29–45.

30. Onoue S, Hashimoto N, Yamada S. Dry powder inhalation systems for pulmonary delivery of therapeutic peptides and proteins. Expert Opin Ther Pat 2008; 18: 429–42.
31. Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. Nat Rev Drug Discov, 2007; 6(1): 67–74.
32. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta2-agonist particle size. Am J Respir Crit Care Med. 2005; 172(12): 1497–1504.
33. Katz IM, Schroeter JD, Martonen TB. Factors affecting the deposition of aerosolized insulin. Diabetes Technol Ther., 2001; 3(3): 387–397.
34. Farr SJ, McElduff A, Mather LE, et al. Pulmonary insulin administration using the AERx system: physiological and physiochemical factors influencing insulin effectiveness in healthy fasting subjects. Diabetes Technol Ther., 2000; 2(2): 185–197.
35. Cynthia L. Stevenson,David B. Bennett. Development of the Exubera® Insulin Pulmonary Delivery System. Mucosal Delivery of Biopharmaceuticals pp 461-481.
36. L. Heinemann New ways of insulin delivery. International Journal of Clinical Practice, Volume 64 – Feb 1, 2010.
37. Affreza. Prescribing Information. MannKind Corporation. Danbury, CT, June 2014.
38. "US Afrezza label" (PDF). FDA. May 2015.
39. Rave K, Heise T, Pfutzner A, Boss AH. Coverage of postprandial blood glucose excursions with inhaled Techno sphere insulin in comparison to subcutaneously injected regular human insulin in subjects with type 2 diabetes. Diabetes Care., 2007; 30(9): 2307-2308.
40. Rosenstock J, Bergenstal R, DeFronzo RA, et al. Efficacy and safety of Technosphere inhaled insulin compared with Techno sphere powder placebo in insulin-naive type 2 diabetes suboptimally controlled with oral agents. Diabetes Care., 2008; 31(11): 2177–2182.
41. Henkin RI. Inhaled insulin for diabetes mellitus. N Engl J Med., 2007; 356: 2107.
42. Henkin RI, Doherty AE, Martin BM. Nasal seroproteins: a new frontier in the exploration of physiology and pathology of nasal and sinus disease. New frontiers in immunobiology in otolaryngology, 2000; 127–52.
43. Dreyer K, Vaag A, Bech K, Hansen P, Sørensen AR, Mygind N. Intranasal administration of insulin with phospholipids as absorption enhancer: pharmacokinetics in normal subjects. Diabet Med., 1992; 9: 335–40.

44. Nam AhKim, Ritu Thapa, Seong Hoon Jeong, Hae duck Bae, Jeehye Maeng, Kyunglim Lee, KinamPark. Enhanced intranasal insulin delivery by formulations and tumor protein-derived protein transduction domain as an absorption enhancer. Journal of Controlled Release, 28 January 2019; 294: 226-236.
45. Moses AC, Gordon GS, Carey MC, Flier JS. Insulin administered intra nasally as an insulin-bile salt aerosol: effectiveness and reproducibility in normal and diabetic subjects. Diabetes, 1983; 32: 1040–7.
46. Saffran M, Kumar G, Savariar C, Burnham J, Williams F, Neckers D. A new approach to the oral administration of insulin and other peptide drugs. Science, 1986; 233: 1081–4.
47. Lassmann-Vaque V, Thiers D, Vialettes B, Vaque P. Preprandial intranasal insulin. Lancet, 1988; 1: 367–8.
48. Frauman AG, Cooper ME, Parsons BJ, Jerums G, Louis WJ. Long term use of intranasal insulin in insulin-dependent diabetic patients. Diabetes Care, 1987; 10: 573–8.
49. Frauman AG, Jerums G, Louis WJ. Effects of intranasal insulin in non-obese type 2 diabetes. Diabetes Res Clin pract, 1987; 3: 197–202.
50. Hilsted J, Madsbad S, Hvidberg A, Rasmussen MH, Krarup T, Ipsen H, et al. Intranasal insulin therapy: the clinical realities. J Control Release, 1996; 41: 69–75.
51. Sarkar MA. Drug metabolism in the nasal mucosa. Pharm Res., 1992; 9: 1–9.
52. Salzman R, Manson JE, Griffing GT, Kimmerle R, Ruderman N, McCall A, et al. Intranasal aerosolized insulin. Mixed-meal studies and long-term use in type I diabetes. N Engl J Med., 1985; 312: 1078–84.
53. Lalej-Bennis D, Boillot J, Bardin C, Zirinis P, Coste A, Escudier E, et al. Six month administration of gelified intranasal insulin in 16 type 1 diabetic patients under multiple injections: efficacy vs subcutaneous injections and local tolerance. Diabetes Metab, 2001; 27: 372–7.
54. Rocío Fernández-Urrusuno, Pilar Calvo, Carmen Remuñán-López, Jose Luis Vila-Jato, María José Alonso. Enhancement of nasal absorption of insulin using chitosan nanoparticles. Pharmaceutical Research, 1999; 16: 1576–81.
55. Illum L. Nasal drug delivery—possibilities, problems and solutions. Journal of Controlled Release, 2003; 87: 187–98.
56. Benedict C, Dodt C, Hallschmid M, Lepiorz M, Fehm H, Born J, et al. Immediate but not long-term intranasal administration of insulin raises blood pressure in human beings. Metabolism, 2005; 54: 1356–61.