



## Recent technologies in insulin delivery systems

### Yeni teknolojilerle insülin uygulama yolları

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#### Abstract

Studies for different ways of insulin delivery have started since the first discovery of insulin. However, desired biological effect of non-parenteral routes has not been achieved, yet. Unfortunately the use of insulin has been limited to parenteral routes due to enzymatic degradation process by mucosal peptidase, mucosal barrier resulting in insufficient absorption and poor permeability throughout the intestinal mucosa. The parenteral route of insulin has been used in different ways including intramuscular, subcutaneous, intravenous and intraperitoneal ways. However, the parenteral route has side effects involving patient's compliance due to fear of injection, local discomfort including bleeding at injection site, injection pain, lipohypertrophy as well as some disadvantages such as glycemic fluctuation. Alternative routes of non-invasive insulin delivery including oral, nasal, buccal, ophthalmic, rectal, vaginal, and transdermal systems have been performed even though successful results have not been achieved due to the above mentioned barriers. Additionally, recently approved technology of insulin delivery through pulmonary route has also been one of the methods aimed at replacing parenteral route. However, recent pulmonary technology of insulin delivery requires higher doses and frequent applications. Furthermore, inhaler insulin is not applicable to smokers and is not used in patients with pulmonary diseases or infections. Today, desired clinical efficacy and safety on the use of non-invasive routes of insulin have not yet been achieved and studies are continuing with newly developed technologies.

**Keywords:** Oral Insulin; Inhaler Insulin; Buccal Insulin; Transdermal Insulin.

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#### Öz

İnsülinin farklı yollardan uygulanması ile ilgili çalışmalar insülinin ilk keşfi ile birlikte başlamıştır. Ancak parenteral yol dışındaki uygulamalarda istenilen biyolojik etki sağlanamamıştır. Ne yazık ki insülinin mukozal peptidazlarla enzimatik yıkıma uğraması, mukozal bariyer nedeni ile yeterli absorpsiyonun olmaması ve intestinal mukoza boyunca absorpsiyonun yetersiz olması kullanımını parenteral yol ile kısıtlamıştır. İnsülinin parenteral kullanımı intramusküler, subkutan, intravenöz ve intraperitoneal olmak üzere farklı şekillerde mümkün olmaktadır. Ancak parenteral uygulamanın enjeksiyon yerinde ağrı, enjeksiyon bölgesinde kanama, lipohipertrofi gibi lokal rahatsızlık verici yan etkileri ve glisemik dalgalanma gibi dezavantajları bulunmaktadır. İnsülin, oral, nazal, bukkal, oftalmik, rektal, vaginal ve transdermal yollardan uygulanmış, ancak bu bariyerler nedeni ile başarılı sonuçlara ulaşılamamıştır. Ek olarak, parenteral uygulama dışında onaylanmış bir diğer insülin uygulama yolu pulmoner yoldur. Ancak bu yeni pulmoner teknoloji yüksek doz ve sık uygulama gerektirmektedir. İlave olarak sigara kullanımında, pulmoner hastalık ve enfeksiyon varlığında kullanılamamaktadır. Bugün, insülinin non-invaziv yollardan kullanımıyla ilgili istenilen klinik etkinlik ve güvenilirlik elde edilememiştir; bu nedenle çalışmalar yeni geliştirilen teknolojiler ile devam etmektedir.

**Anahtar Kelimeler:** Oral İnsülin; Inhaler İnsülin; Bukkal İnsülin; Transdermal İnsülin.

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Studies on insulin administration via different routes started upon the discovery of insulin. As the desired effect could not be obtained with insulin, a peptide molecule, administered via a non-parenteral administration route, using a different route is not possible today. Upon the removal of the first inhaler insulin from the market in 2007, many studies in this field were terminated as they lost sponsorship. While this gave a pause to the studies on administration of insulin via different routes, interest in this subject is gradually increasing with the advancing technologies.

Insulin was first discovered in 1921 by Frederick Grant Banting, John Macleod and Charles Best (1, 2). By subjecting the pancreatic ducts to atrophy, internal secretions were isolated, and obtained extract was given to dogs rendered diabetic by pancreatectomy. By this means, blood glucose was lowered (2). In this review, differences in parenteral administration of insulin and developments in its mucosal use will be discussed.

### 1- Parenteral Insulin Use

While oral route was used in the initial experiments on insulin use, oral administration was found to be ineffective due to intestinal enzymes. Intramuscular route was used for the first insulin administration. As it was found that subcutaneous administration is as effective as intramuscular route and causes less pain, subcutaneous route was started to be used (3). Subcutaneous insulin use was also improved over the years. With cartridge pens in early on, and disposable pens and jet injectors in the later years, insulin was rendered more practical. Today, reusable pens by Owen Mumford, Lily and Novo Nordisk are being used. They are specifically used for short-acting and intermediate-acting insulin only. Reusable insulin pens require insulin cartridges. For disposable insulin pens, no cartridge or reservoir is necessary. The pen is disposed when it is expired or when its use is finished. Today, there are 3 types of disposable pens used. These include kwickpen by Lily Company, solostar pens by Sanofi Company and flexpen by Novo Nordisk. Also, flextouch pens by Novo nordisk which were approved in 2013 by FDA are being used abroad. Its difference from flexpen pens is the lack of dose button extension and being able to be used with low pressure independent from dose. Disposable pens enable the use of 60-80 units of insulin by single injection (4).

Being used as an alternative in insulin administration today, insulin infusion pumps are being used as removable and implantable, programmable infusion pumps (5, 6). Insulin reservoir is delivered from reservoir into subcutaneous tissue via catheter and needle (5, 6). Using pump system, basal insulin can be titrated at 0.25 intervals and bolus insulin at 0.05 intervals, thereby, minimizing blood glucose fluctuations (7). V-Go devices are disposable insulin pumps. They are used daily and changed every 24 hours. As it involves manual

application, it is attached on a visible and accessible part of the body (abdominal skin) (8). Recently became available, Omnipod insulin pump is a wireless insulin pump without the need of separate infusion set use. Its advantages include being water resistant, and being able to be used during bath or in pool (9, 10).

Implantable insulin pumps are mostly administered via peritoneal route (11). As programmable implantable medical systems (PIMS) with battery life of up to 5 years, they provide pulsatile insulin release. It has been reported to reduce blood glucose fluctuations and hypoglycemia risk; however, as catheter blockage was observed due to omental tissue capsulation, the use of implantable pumps is restricted (12). Being the most recent one among these systems, Diaport systems involve an externally placed pump and percutaneous port. As insulin directly reaches to portal system through intraperitoneal infusion, it has been reported that peripheral hyperinsulinemia is reduced, and glucagon response and hepatic response to hypoglycemia are improved (13).

### 2- Mucosal Insulin Use

Nasal, pulmonary, oral, buccal, opthalmic, rectal, and vaginal use of insulin have been studied, however, desired efficacy could not be obtained.

#### a- Pulmonary use

Initial studies with aerosol insulin started in 1920s (14). Interest in inhaler insulin increased again in 1970s, and hypoglycemic effect was obtained in rabbits (15). However, use of inhaler insulin did not start until 2006. For the first inhaler insulin, FDA approval was granted in January 2006 (16). Studies in those years using inhaler insulin reported a considerable improvement in fasting and post-prandial glucose levels and HbA1c, and a considerable decrease in hypoglycemia. However, due to inhaler insulin which is recombinant human insulin being impractical to use (difficulty in blister placement into the device, difficulty in activating the airway, inability to select certain insulin dose, the device being inconvenient, effort put in teaching how to use it), adverse effects such as blindness though temporary, high cost, low demand and failing to obtain expected sales, it was removed from the market in October 2007 after 1 year of use (17, 18).

Pulmonary administration provides an almost 95% absorption area with its 140 m<sup>2</sup> large surface area, thin alveolar epithelium (0.1–0.2 μm), sufficient vascularization and minimal mucociliary clearance mechanism (19). However, as in the clinical trials using this medication, lung cancer was observed more frequently in the group using inhaler insulin, FDA issued a warning regarding this cancer for individuals using inhaler insulin with the history of smoking in April 2008. Upon the completion of clinical trials, it has also been reported that lung cancer was observed more compared to the control group in the FUSE study in which these patients were followed up for 2 years (Table 1) (20).

**Table 1.** Results of the FUSE study in which patients using inhaler insulin were followed up for 2 years

	Patients using inhaler insulin	Control group
Number of participants	3875	3564
The rate of lung cancer (Diagnosis/1000) patient years	1.07	0.29
The rate of all-cause mortality (Mortality/1000) patient years	6.03	7.37
The rate of lung cancer-related mortality (Mortality/1000) patient years	0.48	0.17

Upon the removal of inhaler insulin from the market, many studies ongoing in this field were terminated due to the lack of sponsorship. However, Mankind continued studies using dry powder inhaler insulin using technosphere technology (21, 22). Technosphere technology is the system involving the delivery of insulin in very small size using fumaryl diketopiperazine molecules and polysorbate 80. By this means, insulin molecules with the diameter of 2.5 micron can be delivered up to basal parts of pulmonary systems (23, 24). Via the inhalation of technosphere insulin, serum insulin concentration rapidly increases within 5 minutes and peaks in 15-30 minutes (25). Almost all insulin dose can be cleared from lungs within 12 hours (21). Therefore, pulmonary adverse events are expected to be lower. In clinical trials, it has been reported that 2 patients were diagnosed with lung cancer, other 2 patients were diagnosed with lung cancer after the end of the study, however, these results are found insufficient to detect its association with pulmonary malignancy (26). Technosphere insulin has been approved by FDA in June 2014. However, FDA requested post-marketing studies with larger populations in which the risk of pulmonary malignancy and pulmonary functions are assessed.

#### b- Oral use

For the successful distribution of protein- and peptide-structured molecules from gastrointestinal system;

- It should be protected from enzymatic degradation in GIS
- It should pass the intestinal barrier
- It should be integrated to systemic circulation

To overcome these barriers;

Enzyme inhibitors

Absorption enhancers

Novel polymeric systems

Chemical exchange methods are being used (27).

Using oral insulin, the aim is to provide a non-invasive treatment with high patient compliance, allowing early insulinization, inhibiting gluconeogenesis in liver by portal circulation and protecting against peripheral hyperinsulinemia.

The prominent ones among these insulins studied in ongoing clinical trials are discussed below.

**Biocan-IN-105:** It was created by conjugating the IN-105 human insulin molecule at position 29 with polyethylene glycol via acyl chain.

In Phase 1 and 2 studies, it has been demonstrated to reduce blood glucose (28, 29), however, did not provide significant decrease in the post-prandial glucose level in the Phase 3 trial.

**Capsulin-diabetology:** It is the oral version of insulin aspart, rapid-acting insulin. It contains molecule stabilizer, absorption enhancer and enteric coating. Coating is dissolved in jejunum at neutral pH and its capsule content is released. In the Phase 2a study performed in 16 type 2 diabetic patients in 2010, capsulin insulin has been found to be safe; however, the dose has been reported to be suboptimal (30). No new studies have been reported since Phase 2a studies.

**Diasome-hepatic directed vesicle insulin:** It contains insulin and hepatic specific molecule between two phospholipid layers. It is lyosomal oral insulin with the molecular volume below 150 nanometers. It has a formulation converting hepatic glucose outcome to hepatic glucose intake. It is produced in 2 forms, subcutaneous and oral gel capsule. While high doses are needed to reach the desired bioavailability for many drug technologies, it is possible to obtain the desired effect also with low doses using this technology. The required insulin dose is exactly same with the dose of subcutaneous insulin (31).

**Oramed insulin:** It is produced as capsule containing enteric coating, absorption enhancer and protease inhibitor. It has been observed to be tolerated well in Phase 2a studies, and provide effective blood glucose decrease and improvement in insulin and C-peptide response, and no serious adverse event has been reported. Data of Phase 2b study in Type 1 diabetics have yet to be published.

**Oral-lyn:** Currently being studied by Generex Company in another platform, "oral-lyn" technology which is used as oral or buccal spray consists of combination of surfactant, solvent, micel-forming agent and emulsifier (32). Its biokinetic properties are similar to synthetic rapid-acting insulin analogs. Phase 3 studies are currently ongoing (33).

**c- Transdermal insulin:** Transdermal insulin use also started to be applied with today's advancing technology. The largest barrier against transdermal administration of a large peptide molecule like insulin is the stratum corneum consisting of almost 20 layers. Overcoming this barrier is only possible via active transport of insulin by creating mechanical or chemical injury. Today, insulin can be delivered into systemic circulation via active transdermal systems containing ultrasound or electrical stimuli.

**-Electroporation or permeabilisation:** It is a system based on temporarily permeability increase in membrane using single or multiple short-term, high-voltage pulsed current. While only low-weight molecules can be transferred using electroporation method, absorption-

enhancing molecules such as lipid are needed to be used for the transfer of insulin molecule (34, 35).

**-Iontophoresis:** They are systems facilitating the passage of transdermal insulin using small, low-amplitude electric waves (36).

**-Ultrasonographic devices:** Dermosonic U-systems: These systems are designed as transdermal ultrasonic devices (u-strip) containing 4 transducers coiled on patch powered by battery. They show prominence in transdermal administration. They allow transdermal insulin passage by enlarging sweat and hair follicle pores. Enlargement of sweat glands in dermis provides a store for insulin, thereby a slower release. Patches are designed to contain 20-100 U of insulin. It has a 3-day use period. Basal dose can be transported at 0.25-1 unit intervals per hour. For bolus dose, transport of insulin up to 8 units within 30 minutes has been reported. In clinical trials, blood glucose lowering was comparable to subcutaneous insulin pump in type 2 diabetics, and normal glucose levels were observed throughout the day. Ultrasonic wave volume, bothersome temperature rise or skin damage have not been reported. Phase 2 clinical trials are currently ongoing. Today, non-parenteral use of insulin became possible with inhaler insulin. Studies on pulmonary safety of inhaler insulin are yet to be published. Studies to facilitate the parenteral administration of insulin and studies on its non-invasive mucosal use are currently ongoing.

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