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Pulmonary Delivery as a Route for Insulin

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Abstract: The pulmonary route of administration offers several advantages. First, the lung has a large surface area for drug absorption, ranging from 100 to 140 m^2. In addition, the alveolar epithelium has permeability that allows for rapid absorption of solutes. Because the mucociliary clearance of the alveolar lung tissue is slower than that of the bronchiolar tissues, the alveoli provide a greater opportunity for the absorption of larger molecules (e.g., insulin). Studies have shown that particle size should be between 1 and 3 micrometers in diameter for optimal deposition in the lung, and that dry powder formulation can deliver more active drug in a single inhalation than liquid aerosol formulations. Patient-controlled variables (e.g., inhalation flow rate, inhaled volume, and duration of inhalation) also need to be controlled for optimal deep-lung insulin delivery. The pharmacodynamic effects of insulin formulations administered via the lung are comparable to, or even faster than, those of subcutaneous injected regular insulin or rapid-acting insulin analogues.

Keywords: transmembrane, mucociliary, liquid aerosol formulations, inhalation, insulin delivery.

Introduction: Oral delivery is the most convenient and the most acceptable route. However, insulin by itself is degraded by intestinal enzymes and is not absorbed intact across the gastrointestinal mucosa. Now, a day gelatin, trypsin coated capsule, pill, pellets may be available. It has some disadvantages, a lot of the insulin will be wasted before it gets where it's going. Insulin taken as a pill is quickly broken down in the stomach, just like the food you eat. That makes it useless for lowering blood glucose levels [1].

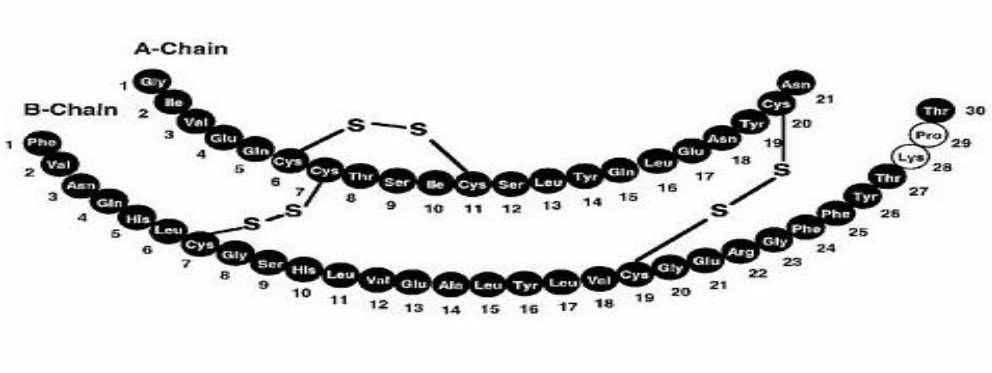


Figure: structure of insulin

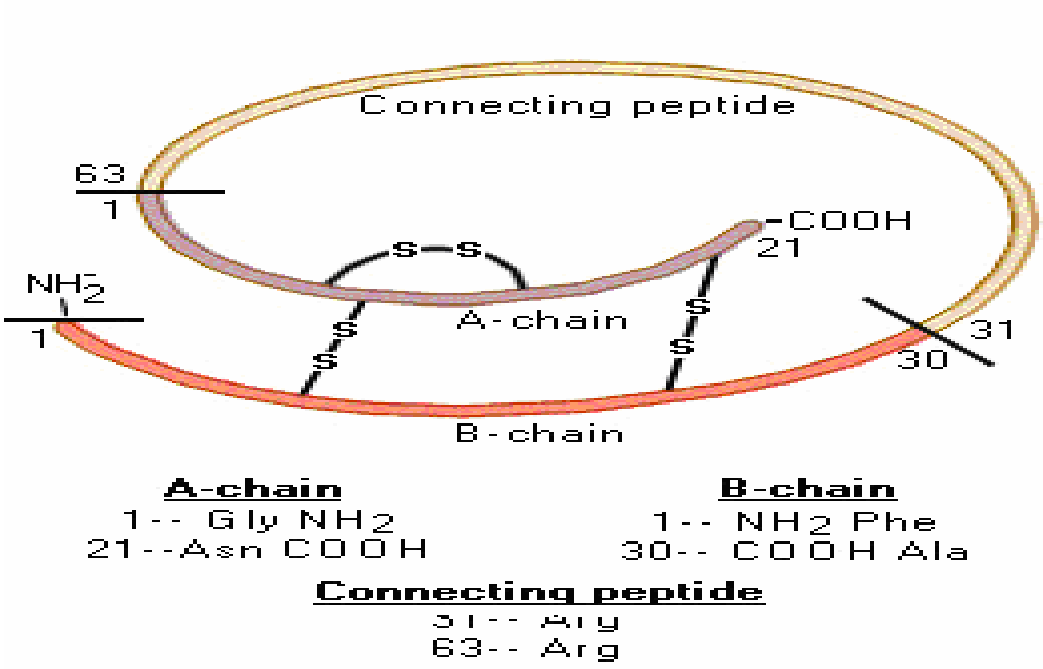


Figure: Structure of Proinsulin

Mechanism of Action of Insulin: Insulin acts on specific receptors located on cell membrane of particularly all cell type: liver, muscle and fat cells are very rich. The insulin receptor consists of and 2 subunits, the subunits are entirely extracellular and contain insulin-binding domain while 2 subunits are transmembrane proteins and possess tyrosine protein kinase activity. Binding of insulin to subunits induces aggregation and internalization of the rooter along with the bound insulin molecules. This activates the tyrosine kinase activity of the 2 subunits. This initiates a complex cascade of biochemical interactions that result in several physiological, biochemical and molecular events. After internalization, the receptor may be degraded or recycled back to the cell surface. Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporters (GLUT). Genes for a large number of enzymes and carriers have been show to be regulated by insulin [5].

Respiratory system: The human respiratory system is a complicated organ system of very close structure–function relationships. The system consisted of two regions: the conducting airway and the respiratory region. The airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs. [16]

Formulations: The drugs can be administered by pulmonary route utilizing two techniques: aerosol inhalation (also used in intranasal applications) and intratracheal instillation. By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs. In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs. [16]

Aerosols: Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols are deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion.

Although there is similarity in drug absorption from the lungs and the other mucosal surfaces, but due to the complexity in aerosol-particle disposition, the aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract. Other factors, which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles.

The devices that are used to produced aerosolization are called as: Inhalers

Types of Inhalers: Inhalers are hand-held devices used for delivering respiratory medication. Although many different styles of inhalers are available, there are two basic types of inhalers:

- Nebulizers (solutions)
- Metered-dose inhalers
- Dry powder inhalers

The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs.

Metered-Dose Inhalers: Metered-dose inhalers use chemical propellants to expel the medication from the inhaler device. To administer the medication, the patient may either use direct inhalation or squeeze the inhaler's canister. MDIs utilize propellants (chlorofluorocarbons and, increasingly, hydrofluoroalkanes) to atomize the drug solution.

Nebulizers: Nebulizers convert medication into a fine mist and deliver the medication through a face mask that covers the mouth and nose. All of which may contain nanostructures such as liposomes, micelles, nanoparticles and dendrimers.

Recently, a number of add-a-device or also called as spacers are added to use with MDIs, in order to remove some non-respirable particles by impaction on their walls and valves. 3M Drug Delivery Systems has recently introduced actuators that will make pulmonary and nasal MDIs more effective and efficient by increasing the respirable fraction of the drug delivered. This will also reduce the side effects

Almost all aerosols were using a CFC (chlorofluorocarbon) propellant but in mid-nineties efforts were made to consider an alternative to ozone depleting CFC by other classes of environmental friendly propellants such as hydrofluroalkanes (HFAs: HFA – 134a and HFA-227). These HFA compounds contain no chlorine, which infact causing the ozone depletion effect. The safety and efficacy of these new introduced propellants were investigated to meet the requirements of American and European regulatory agencies. In most cases, these two propellants met the safety conditions and found that they have safety compliance as of their predecessor CFC propellant. In recent years, many MDIs and DPIs containing CFC were replaced by HFAs [16].

Pharmacokinetic Consideration: In humans, inhaled regular insulin is more rapidly absorbed than insulin from the subcutaneous injection site The duration of action of inhaled insulin is slightly longer than that following subcutaneous administration of insulin lispro or insulin as part (four to six hours versus three to five hours, respectively) but is slightly shorter than the duration of action of subcutaneous administration of regular insulin [15].

Patient Acceptance and Compliance:
Results of numerous clinical trials with inhaled insulin have shown a high degree of patient compliance and acceptance. Preliminary data indicate that patients converting from insulin injections to inhaled insulin (via AERx iDMS) showed higher compliance, demonstrated by improved glycemic control [15].

Factors Affecting the Pulmonary Delivery of Insulin:

- During breathing, drug particles pass, along with air, from the upper airways (oropharynx and larynx) to the lower airways. The lower airways start in the trachea and are followed by successive bifurcations into bronchi and bronchioles within the lungs.
- The rate of drug absorption is expected to vary at different sites within the lungs due to the variable thickness of the mucosal surface.
- There is a steep increase in the surface area of the lungs within the alveolar region, which is the target site for drug deposition when systemic drug absorption is desired.
- The mode of inhalation and aerosol properties, influence the deposition of drugs within the respiratory tract.
- The most important features of inhalation affecting drug deposition are inhaled volume, flow rate [10].

The ideal size for pulmonary delivery of particles into the deep lung region is between 1 and 5 μm in geometric diameter, assuming the density of the particle is 1 g/cm^3. However, aerodynamic diameter rather than geometric diameter controls particle deposition in the lungs. Aerodynamic diameter is a product of geometric diameter and the square root of density. When a particle becomes more porous, it becomes lighter in density, and the overall aerodynamic diameter decreases. Thus, as particle density decreases, particles that are larger in geometric diameter can deposit into the deep lung region. Throughout this article, particle size and particle diameter represent geometric diameter, unless stated otherwise [9].

Pulmonary Inhaler Development

Inhaler Design:
Typical limitations of traditional inhalation devices include low efficiency, variable dosing, poor moisture barriers, low drug content per inhalation, inapplicability

to macromolecules, and sensitivity to the breathing maneuver. In comparison, the EXUBERA inhaler is a novel pulmonary delivery system developed by Nektar Therapeutics that solves many of these challenges. The pulmonary delivery system is a reusable dry powder inhaler that has been designed to deliver insulin to the small airways and alveoli for systemic insulin absorption [2].

The inhaler was designed to provide reproducible powder extraction, deagglomeration, and dispersion, capable of aerosolizing relatively small amounts of cohesive powder (1–10) mg. It is solely mechanical, and requires only modest effort by the patient to operate. Unlike typical high-resistance inhaler systems, aerosolization of insulin powder is independent of patient inspiratory effort, providing opportunities for improved performance and product consistency [2].

The inhaler consists of three subsystems: base, Trans Jector, and chamber/mouthpiece. The inhaler performs four key functions: puncture of the insulin powder-containing blister after loading into the device, extraction of the powder from the blister, dispersal of the powder into the chamber, and facilitation of inhalation delivery of the powder cloud to the patient [9].

Specifically, the base contains an air pump and valves that generate, store, and release compressed air. Upon actuation, an individual blister is punctured; and compressed air is released through a jet structure in the Trans-Jected and then vented into the chamber. The sudden sonic discharge of this mass of air through the small jets in the Trans-Jector results in extraction and dispersion of insulin powder [11].

The rapidly moving air creates a vacuum in the TransJector and blister, causing the insulin powder to be drawn into the chamber and dispersed into a cloud after the aerosol cloud has formed in the chamber, the patient rotates he mouthpiece 180° into the open position and inhales the dose. The emitted dose, particle size distribution, and fine particle dose of the aerosol are controlled primarily by characteristics of the insulin powder and the inhaler, and are relatively independent of variables that may be introduced by the patient. The inhaler was specifically designed such that patients can use the device with a simple, slow, deep inhalation [2].

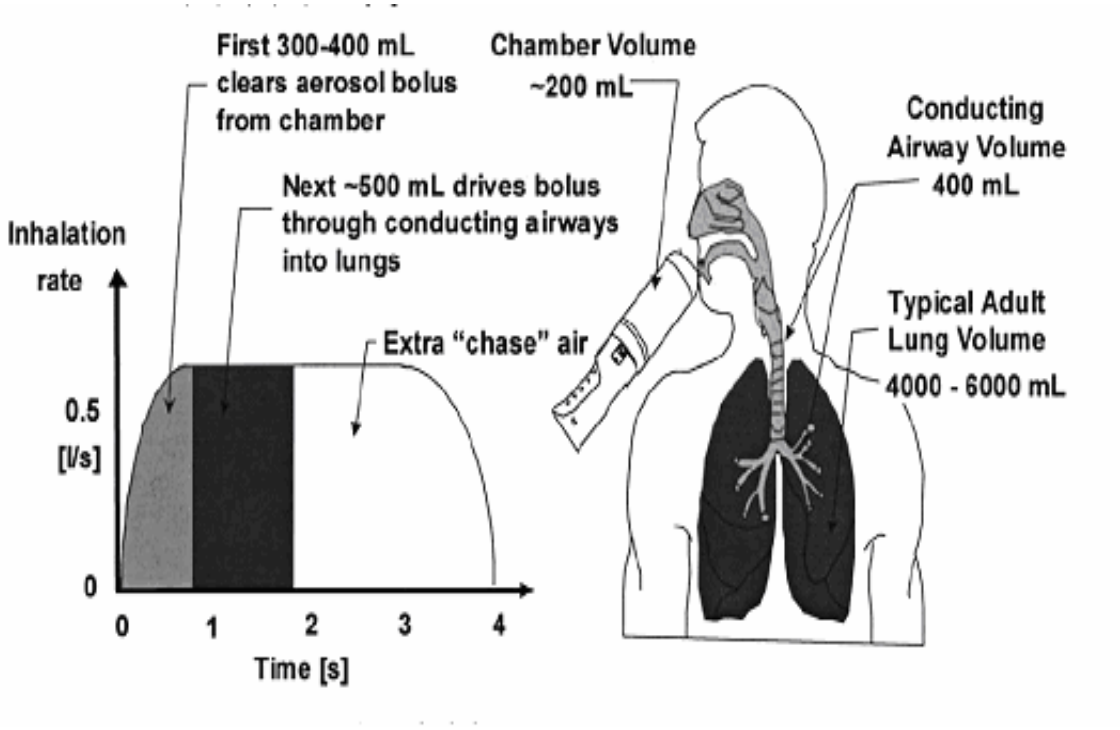


Figure. Aerosol inhalation ex-pulmonary delivery system.

Inhaler Performance:

Insulin powder is delivered into the deep lung .Dosing occurs during emptying of the chamber volume (200 mL), specifically within the first 300–400 mL of the inhalation breath.

The following 500 mL of inhalation volume moves the dose through the conducting airways into the deep lung.

Spray dried powder primary particle size distribution is measured by laser light scattering following high-energy pneumatic dispersion, and the corresponding aerosolized powder (ex-device) is measured by cascade impaction. This minor shift in particle size distribution is consistent with the powder being predominately dispersed to primary particles in the inhaler-aerosolized cloud [3].

Dry Insulin Powder for Inhalation: Pulmonary administration of drugs is convenient and enables patients to avoid the need for painful injections. Recently, the pulmonary route has attracted attention as a noninvasive systemic administration route for peptide and protein drugs. However, pulmonary bioavailability of macromolecules is still below intravenous or subcutaneous bioavailability. There have so far appeared many reports on the enhancement of pulmonary absorption of peptides and proteins. In these reports, bile acids, surfactants, fatty acids, citric acid, and protease inhibitors.

Proteins and peptides are often formulated with sugars, such as lactose, trehalose, and mannitol, to protect them from degradation during the spray drying process, freeze-drying process, and storage.

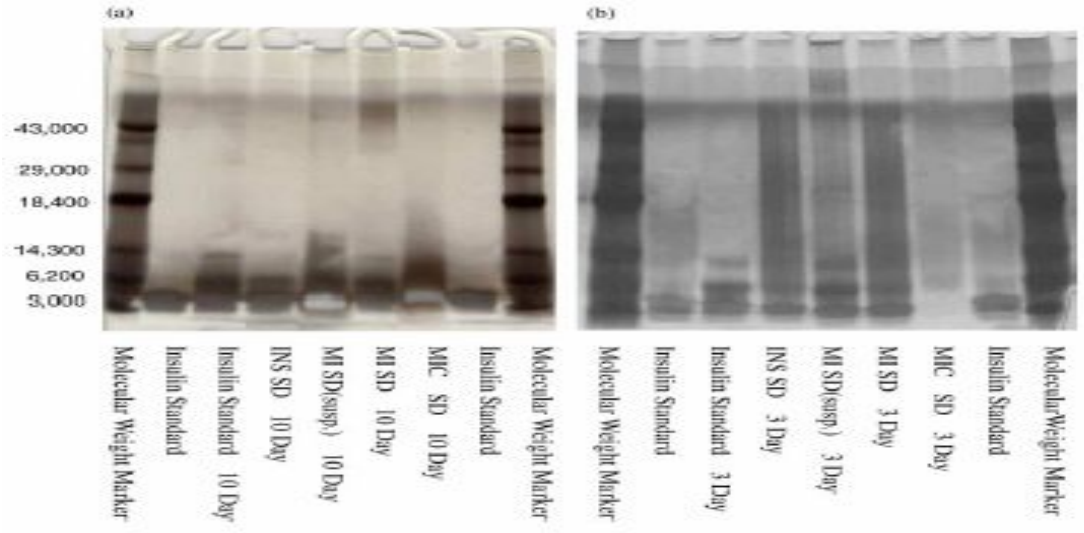
Powder Production: Insulin powders were made by dissolving bulk crystalline insulin in sodium citrate buffer containing excipient (mannitol, or raffinose, or none) to give final solids concentration of 7.5 mg/ml and a pH of 6.7±0.3. The spray dryer was operated with an inlet temperature between 110°C to 120°C and a liquid feed rate of 5 ml/min, resulting in an outlet temperature between 70°C and 80°C. The solutions were then filtered through a 0.22 μm filter and spray dried in a Buchi Spray Dryer to form a fine white amorphous powder. The resulting powders were stored in tightly capped containers in a dry environment (<10% RH) [4].

Preparation of Insulin Powder Using a Spray –drying Technique:

Insulin suspensions and solutions were prepared by adding insulin with or without additives to distilled water. Insulin was suspended by simply adding to water. The decrease in pH of the insulin suspension. Below the isoelectric point (5.0–5.3) with a 1.0M HCl solution and the successive increase in the pH to.4 with a 1.0M NaOH solution gave an insulin solution. The addition of citric acid to an insulin Suspension resulted in the dissolution of insulin, while it was still suspended after the addition of bacitracin or Span 85. The preparation of dry insulin powders by a spray drying technique was reported in our previous report. Briefly, the following standard operating conditions were used for spray-drying with an SD-1000 spray-drier an inlet temperature of 90 °C, a drying air flow rate of 0.75ml/min, a solution feed rate of 5 ml/min, and an atomizing air pressure of 100 kPa. Operating under these conditions resulted in an outlet temperature 63–69 °C. The code names and compositions of the formulations are listed in Table 10.2. The dry powder INS SD was prepared from 1.0% insulin solution. The dry powders MI SD (susp) and MI SD were prepared by spray drying a 0.25% insulin suspension and 0.25% insulin solution, respectively, containing 5.0% mannitol. The dry powder MIC SD was manufactured with 0.25% insulin solution containing 0.20% citric acid and 5.0% mannitol. MIB SD and MIS SD were manufactured with 0.25% insulin suspension containing 10mM bacitracin and 1.0% Span 85, respectively, and 5.0% mannitol. The dry powder MI_ was prepared by spray drying a 0.5% insulin suspension containing 5.0% mannitol. MC was prepared by spray drying a 0.40% citric acid and 5.0% mannitol solution without insulin [6].

Insulin Absorption After Intratracheal Administration of MIC MIX:

The hypoglycemic effect of MIC Mix after pulmonary administration to the rat lung was examined and compared with those of INS SD, MI SD, MI SD (suspension), and MIC SD.MIC Mix showed a rapid onset and elongated hypoglycemic effect compared its INS SD, MI SD (suspension) and MI SD. There was no significant difference observed between MIC SD and MIC Mix regarding the decrease in the plasma glucose level at each time point, suggesting the combination of insulin and citric acid powders was as effective as the dry insulin powder containing citric acid [7].



Pharmacokinetic study:

A variety of short human studies have shown that regular insulin formulations are well absorbed by the lungs. All studies have used regular, soluble insulin.

Future Aspects: According to the World Health Organization (WHO), the global prevalence of diabetes is expected to reach 336.0 million by the year 2030. Diabetes incidence and prevalence are expected to increase by 21.0 per cent in the next 20 years. It is posing a great burden on the limited government health care budgets. It is estimated that EU spends 29.00 billion Euros towards diabetes care costs. The increasing costs due to diabetes and its complications are likely to increase at a geometric progression in the coming years unless measures are taken to control it [16]. The current treatment options available for diabetes are inadequate to meet the needs of the diabetic patient. Disease awareness, lifestyle changes and more compliant treatment methods are the pressing need of the day. The European governments are taking initiatives to increase awareness and education programs. The importance of lifestyle modifications and strict treatment regimen is emphasized [11].

Attempts are being made to reduce the burden of the insulin taking diabetics. Various options for insulin delivery are currently under research to replace the vintage concept of subcutaneous insulin delivery. Oral insulin, Transdermal insulin and diabetes vaccines are in various phases of research. Nanotechnology is presently being utilized to enable better insulin delivery. This technology has tremendous potential to change the face of insulin delivery. The human genome project has opened up avenues for gene therapy. Gene therapy for diabetes is being given much importance owing to the detection of the diabetes gene. But the research is still in the initial stages of development. As diabetes is a multigene disorder, the approach is likely to consume more time to succeed [12].

Conclusion: Although the hypoglycemic effect was greatly improved when the dry insulin powder with citric acid (MIC SD) was administered, insulin in the MIC SD was unstable compared with the other powders. We designed the dosage form to improve the insulin stability without loss of hypoglycemic activity. MIC Mix was formulated as a combination of insulin powder (MI) and citric acid powder (MC). MIC Mix showed hypoglycemic activity comparable to MIC SD and improved insulin stability. In this study, moisture affected the insulin stability and particle morphology. It was suggested that a package preventing moisture absorption was necessary for insulin powders prepared with citric acid.

Table Formulation, sprayed volume, and yield of dry powder:

Formulation code	Insulin state[a]	Mannitol (%)	Insulin (%)	Enhancer	Sprayed volume (ml)	Yield[b] (%)
INS SD	Dissolved	–	1.0	–	100	25.6
MI SD (susp.)	Suspended	5.0	0.25	–	100	44.2
MI SD	Dissolved	5.0	0.25	–	100	44.0
MIC SD	Dissolved	5.0	0.25	0.2% citric acid	100	55.5
MIB SD	Suspended	5.0	0.25	10 mM bacitracin	100	48.7
MIS SD	Suspended	5.0	0.25	1.0% Span 85	100	1.79
MI′	Suspended	5.0	0.50	–	100	40.6
MC	–	5.0	0	0.4% citric acid	100	53.2

a. Insulin state in the stock solution.

b. Yield = amount of powder recovered/amount of ingredients in the sprayed solution.

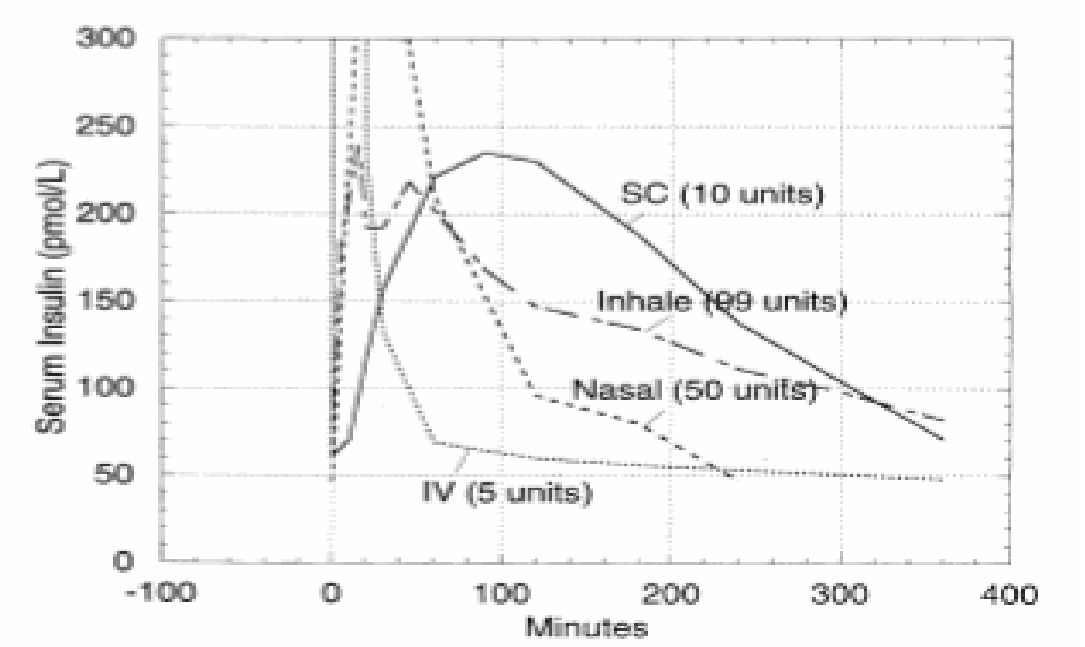


Figure: Comparison of insulin absorption from four different routes of delivery.

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