Routes of Administration
# Alternative Routes of Administration

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- Parenteral administration has disadvantages (needles, sterility, injection skills) compared to other possible routes.

- Therefore, systemic delivery of recombinant proteins by alternative routes of administration (apart from the GI tract, discussed above) has been studied extensively.

- The nose, lungs, rectum, oral cavity, and skin have been selected as potential sites of application.

- The nasal, buccal, rectal, and transdermal routes all have been shown to be of **little** clinical relevance **if systemic action** is required and if simple protein formulations without an **absorption-enhancing technology** are used.

- In general, bioavailability is **too low** and **varies too much.**

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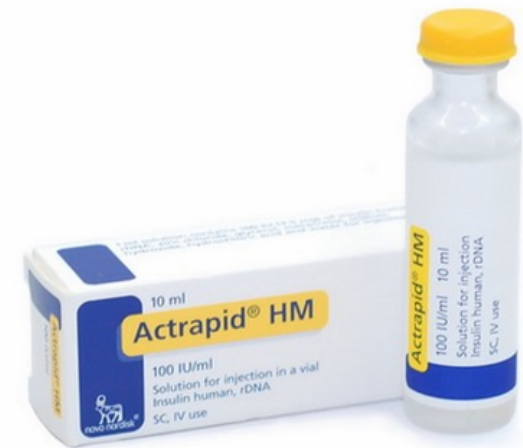
- Intratracheal inhalation or instillation.
- The pulmonary route may be the exception to the rule in the previous slide which states that alternative routes have low bioavailability.
- Table presents the bioavailability in rats of **intratracheally** administered protein solutions with a wide range of **molecular weights**.
- Bioavailability may reach over 50 %.
- **Absorption** was strongly **protein dependent**, with **no clear relationship** with its molecular weight.

Molecule	Mw kDa	#AA	Absolute Bioavailability (%)
α-Interferon	20	165	>56
PTH-84	9	84	>20
PTH-34	4.2	34	40
Calcitonin (human)	3.4	32	17
Calcitonin (salmon)	3.4	32	17
Glucagons	3.4	29	<1
Somatostatin	3.1	28	<1

Adapted from Patton et al. (1994)

PTH recombinant human parathyroid hormone, #AA number of amino acids

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- **Advantages:**

1. Relatively easy to access (aerosol or syringe).
2. Fast uptake.
3. Substantial fractions of insulin are absorbed.
4. Lower proteolytic activity than in the Gl tract.
5. Avoidance of hepatic first pass effect.

- **Disadvantages:**

1. Reproducibility (in particular under pathological conditions, smokers / nonsmokers).
2. Safety (e.g., immunogenicity).
   - presence of macrophages in the lung with high affinity for particulates

- The first pulmonary insulin formulation was approved by FDA in January 2006 **(Exubera®)** but taken off the market in 2008 (by the company) because of poor market penetration.

- Pulmonary inhalation of insulin is specifically indicated for mealtime glucose control.

- Uptake of insulin is faster than after a regular SC. insulin injection (peak 5–60 min vs. 60–180 min).

- The reproducibility of the blood glucose response to inhaled insulin was equivalent to SC-injected insulin.

- But ➔ bioavailability is LOW
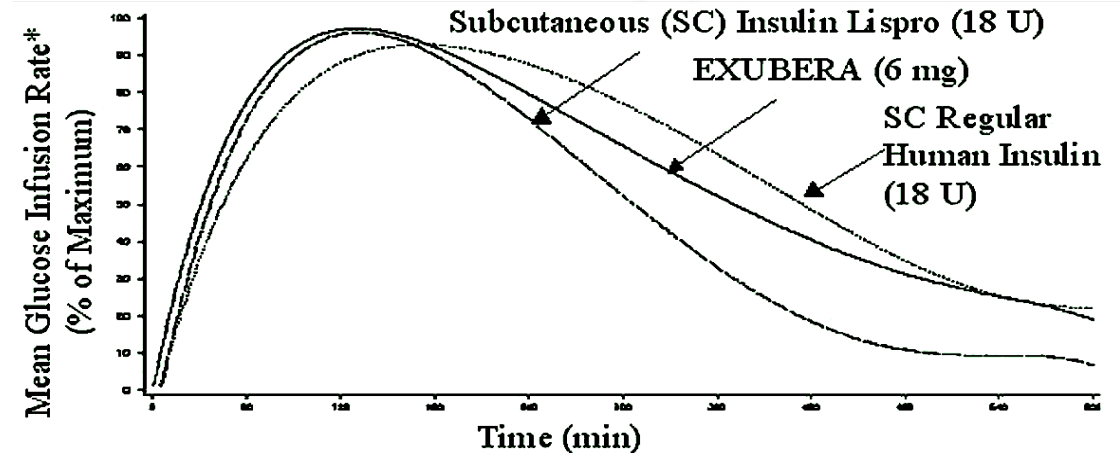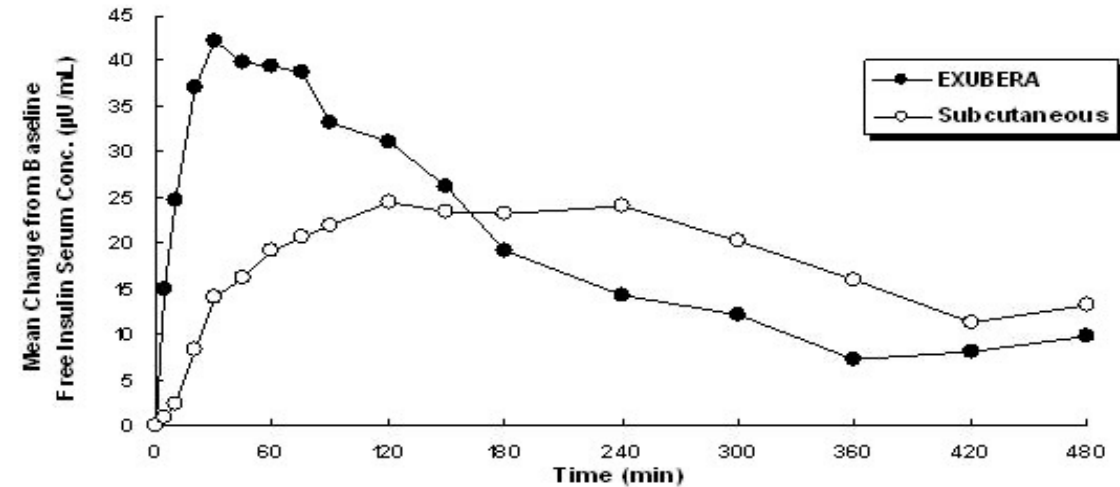
Lispro=Rapid Acting Insulin
6 mg = ~170 IU

1. The fraction of insulin that is absorbed from the lung depends on:
   - The fraction of the inhaled/nebulized dose that is actually leaving the device,
   - The fraction that is actually deposited in the lung,
   - The fraction that is being **absorbed**, i.e., total relative uptake:
   - (TO%) = % uptake from device * % deposited in the lungs * % actually absorbed from the lungs.

   - For the insulin the TO is around 10% and the fraction absorbed from the lung is about 20%.
   - These demonstrate that insulin absorption via the lung may be a promising route, but the fraction absorbed is small and with the Exubera® technology, the patient/medical community preferred parenteral administration.

2. The delivery device was Extremely big and inconvenient for patient to carry. It is also more expensive.

3. There were also concerns about possible dosing errors due to the difference between doses of the inhalable formula versus traditional insulin. This is because SC insulin comes in IU and inhaled insulin in mg which makes confusion for patient and professionals.

4. Insulin needles have become so tiny that most users have no problem with self-injection.

- Approximately one year after introduction into the marketplace, Pfizer announced it would be discontinuing Exubera®, citing that the drug failed to gain market acceptance. With losses of about $1.5 billion

- Therefore, different approaches have been evaluated to increase bioavailability of the pulmonary and other non-parenteral routes of administration.
- The goal is to develop a system that temporarily decreases the absorption barrier resistance with minimum and acceptable safety concerns.
- The mechanistic background of these approaches is given in Table.
- Until now, **no products** utilizing one of these approaches have successfully passed clinical test programs.

Classified according to proposed mechanism of action
Increase the permeability of the absorption barrier:
Addition of fatty acids/phospholipids, bile salts, enamine derivatives of phenylglycine, ester and ether type (non)-ionic detergents, saponins, salicylate derivatives, derivatives of fusidic acid or glycyrrhizinic acid, or methylated β-cyclodextrins
Through iontophoresis
By using liposomes
Decrease peptidase activity at the site of absorption and along the "absorption route": aprotinin, bacitracin, soybean tyrosine inhibitor, boroleucin, borovaline
Enhance resistance against degradation by modification of the molecular structure
Prolongation of exposure time (e.g., bio-adhesion technologies)

- **Advantages:**
- Easily accessible.
- Delivery to a surface area rich in its vascular and lymphatic network.
- Probably lower proteolytic activity than in the Gl tract.
- Bypass of first pass effect.
- **Disadvantages:**
- Reproducibility (in particular under pathological conditions).
- Safety (e.g., ciliary movement), low bioavailability for proteins.
- Short Residence time (less than 30 min)

2,5 ml
Nasal spray
Minirin®
10 microg/dose
(Desmopressin acetate)

FERRING

- Molecular weight was found to be a major factor affecting bioavailability via the intranasal route.

- Polypeptides with a molecular weight of up to 2000 Da were found to be pharmacologically active after nasal administration,

- While peptides and proteins with molecular weights of 2000 – 6000 Da (i.e., insulin, calcitonin, and LH - RH) required the addition of absorption enhancers in order to reach adequate bioavailability.

- **Rectal:**

- **Advantages:**

- Easily accessible, partial avoidance of hepatic first pass, probably lower proteolytic activity than in the upper parts of the Gl tract.

- **Disadvantages:**

- low bioavailability for proteins.

- **Buccal**

- **Advantages**: easily accessible, avoidance of hepatic first pass, probably lower proteolytic activity than in the lower parts of the Gl tract, option to remove formulation if necessary.

- **Disadvantages**: low bioavailability of proteins

- **Transdermal**

- **Advantages**:

- easily accessible, avoidance of hepatic first pass effect, removal of formulation if necessary is possible, sustained/controlled release possible

- **Disadvantages**:

- Low bioavailability of proteins.