

Microneedles for Drug Delivery via Gastrointestinal Tract

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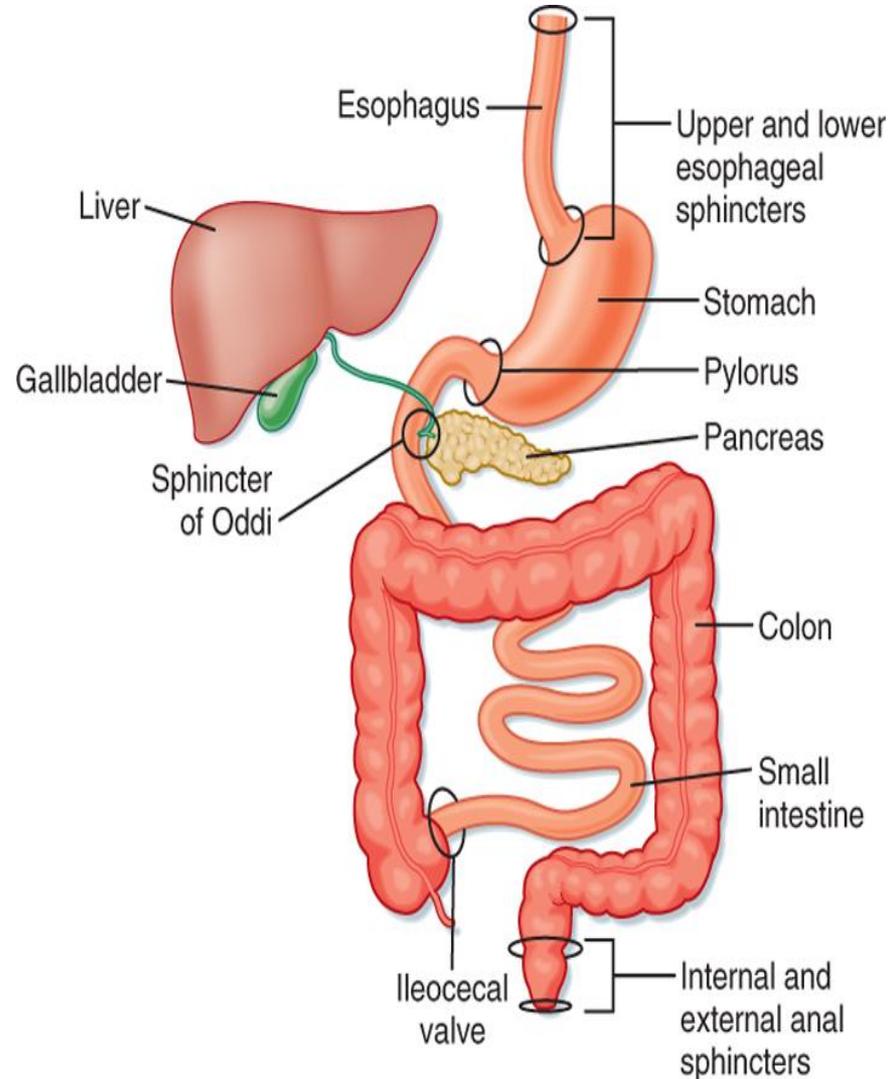
Contents

- Gastrointestinal tract
 - Histology of GI tract
 - Absorption through GI tract
- Drug delivery
 - History of drugs
 - Drug administration
 - Drug delivery routes
- Microneedles
 - History of microneedles
 - Microneedle capsule
 - Advantages of microneedle capsule
- Avenues of exploration
- Inference
- Reference



Gastrointestinal (GI) Tract

- The human gastro-intestinal tract or GI tract, is an organ system responsible for consuming and digesting foodstuffs, absorbing nutrients, and expelling waste.
- Divided into the
 - Upper GI tract – Esophagus and Stomach
 - Lower GI tract – Small intestine and Large intestine



Histology of GI tract

- The whole GI tract consists of four concentric layers called tunics

1. Mucosa

- inner most layer surrounding the lumen
- comes in direct contact with digested food

2. Submucosa

- contains large blood vessels, lymphatics, small glands and nerves branches

3. Muscularis

- consists of an inner circular layer and outer longitudinal muscular layer.
- circular muscle layer prevents food from traveling backward
- longitudinal layer shortens the tract.

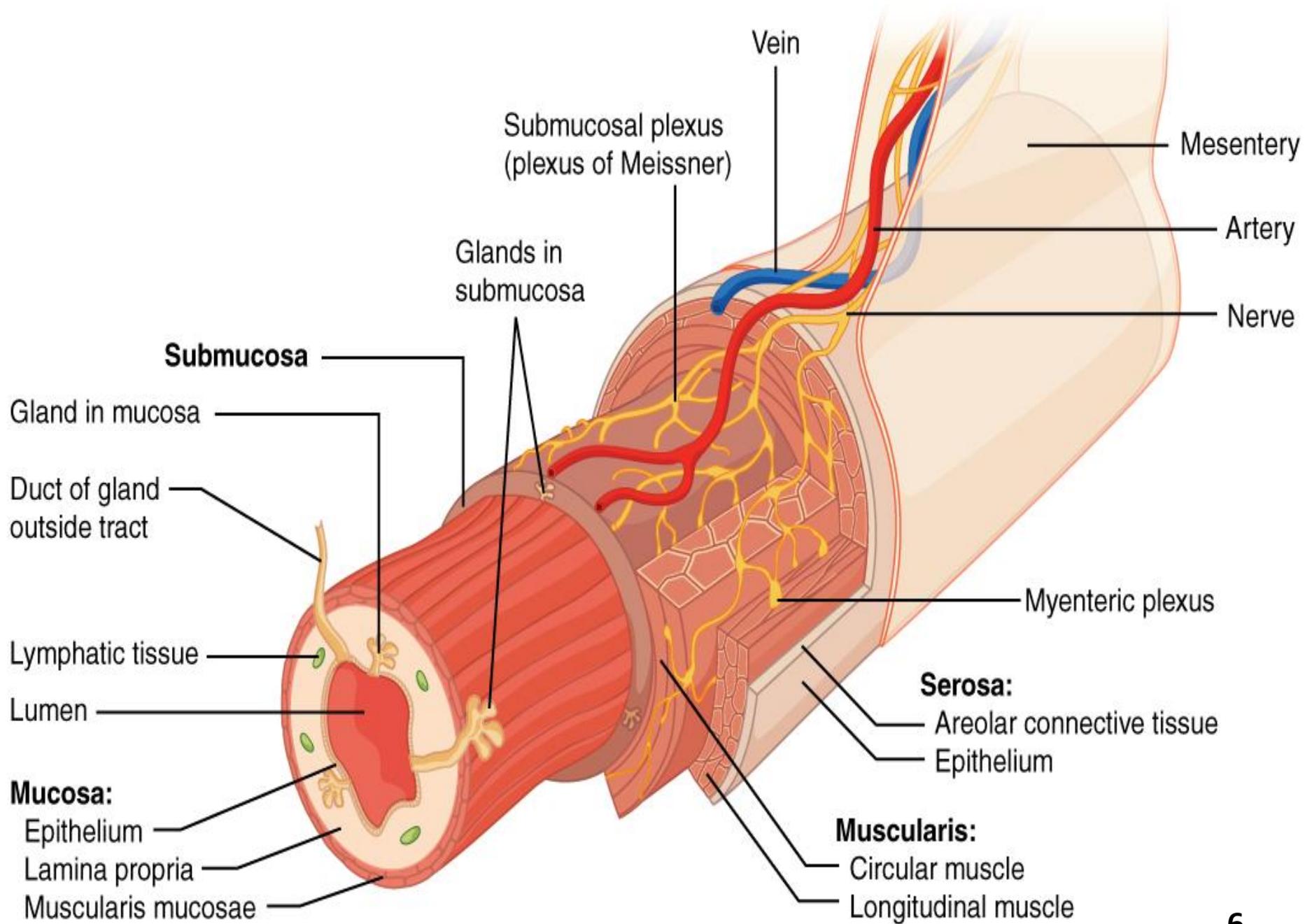


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4. Adventitia or serosa

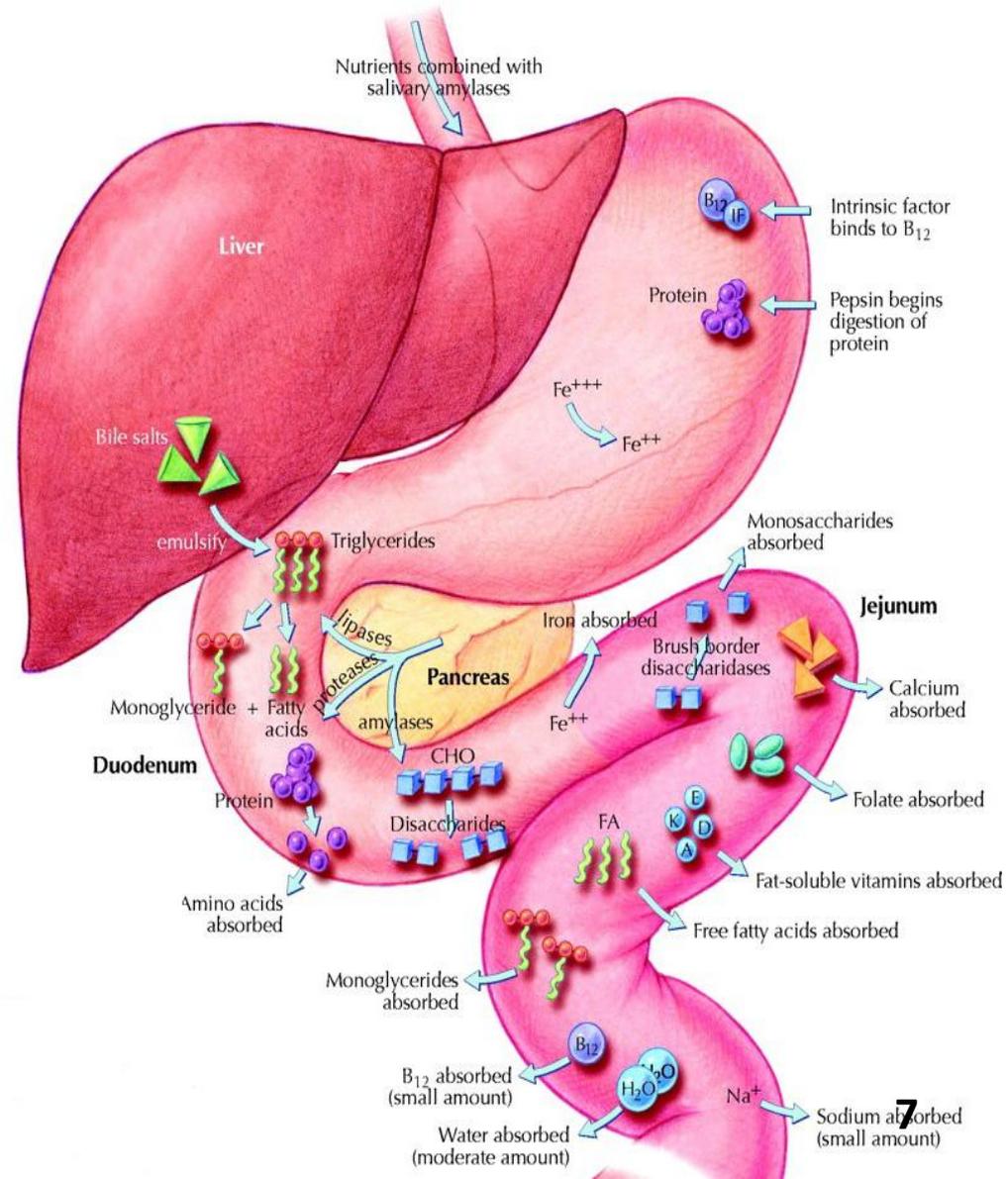
- outer most layer of GI tract
- Differ in form and function according to part of GI tract
- Prevents friction damage from rubbing against other tissues
- The thickness of these tunics and pH varies in different areas of GI tract
 - The normal thickness of stomach ranges between 4 and 6 mm and its pH range is 1-2 (highly acidic)
 - The normal thickness of small intestinal wall is 3-4 mm with pH of 7
 - The colon (large intestine) has thin wall of 2-3 mm and pH of 5.7





Absorption through GI tract

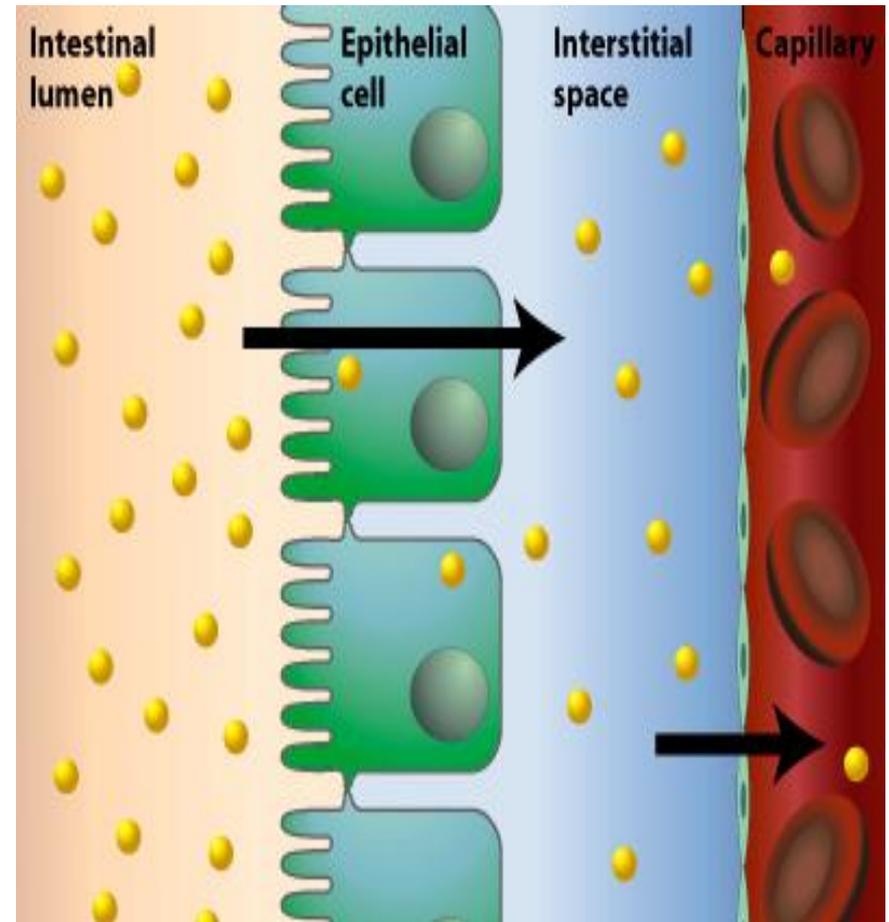
- Absorption is the movement of molecules (either nutrients or drugs) out of the digestive tract and into the circulation.



Molecules pass out of GI tract by

1. Simple diffusion

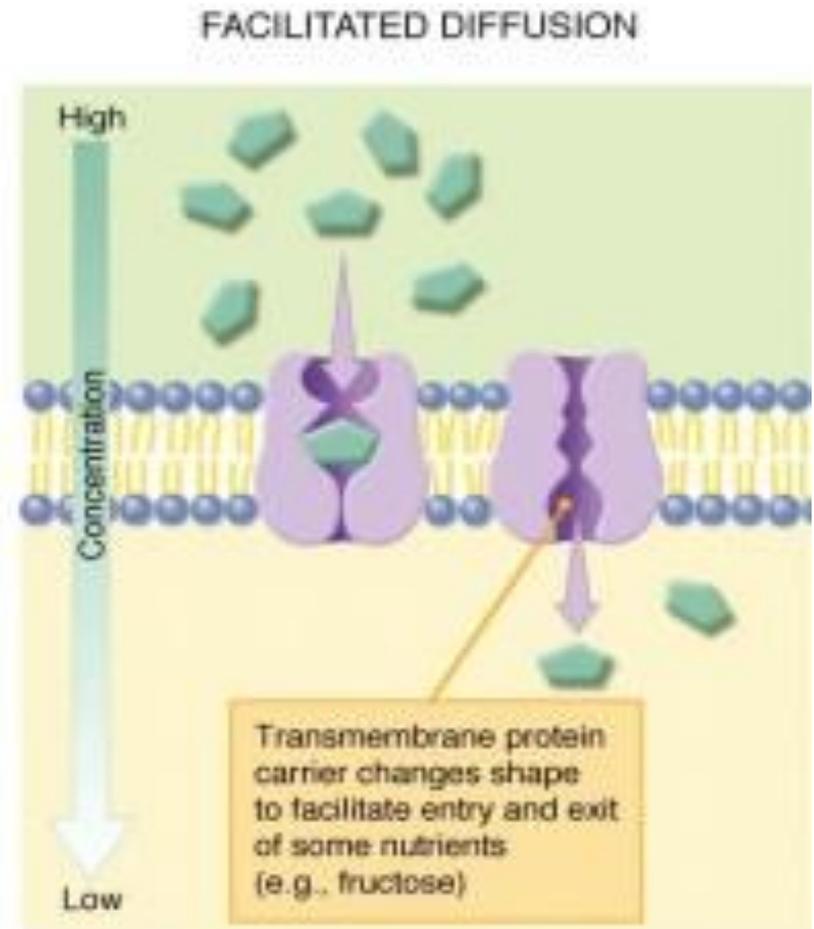
From area of higher concentration to area of lower concentration



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2. Facilitated diffusion

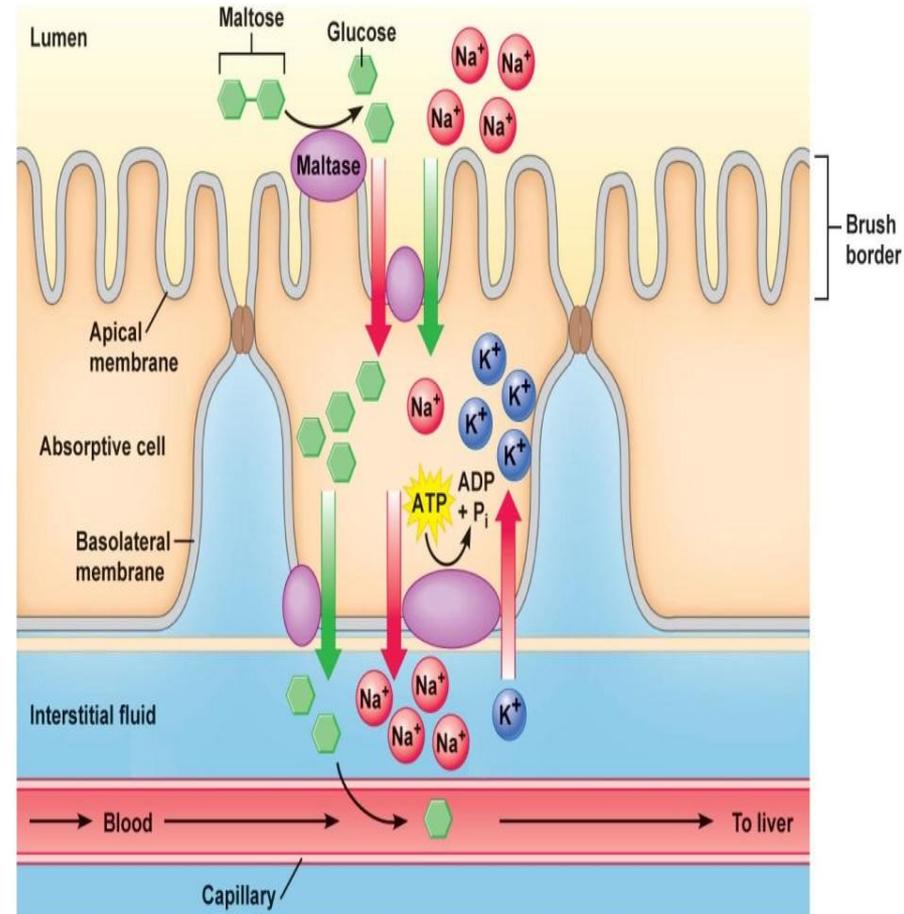
Involves a carrier molecule that combines with the substrate molecule releasing the substrate at other side.



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3. Active transport

Involve transport against a concentration gradient through energy expenditure

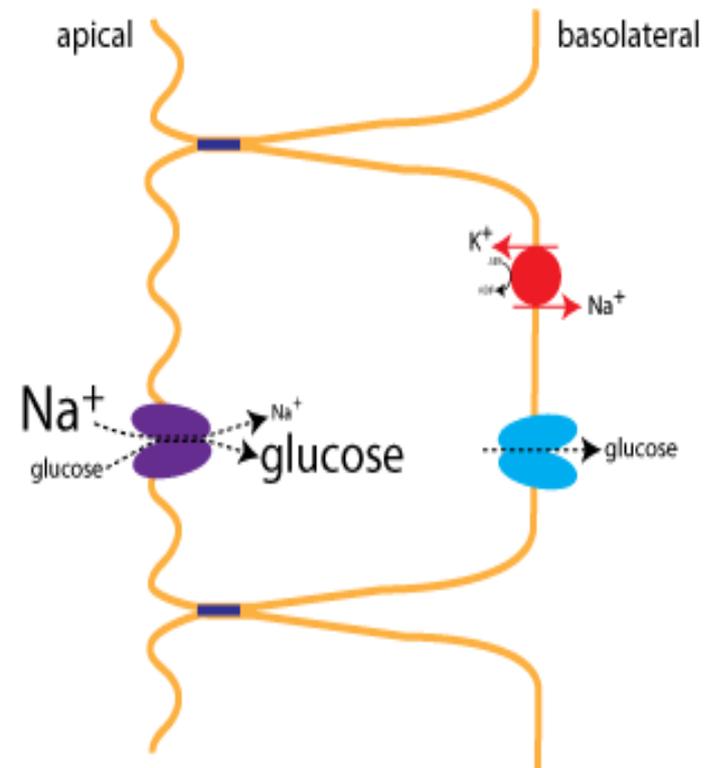


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4. Co-transport

Two substances are simultaneously transported across a membrane by one protein or protein complex



Drug and Drug Delivery

- A **drug** is a chemical substance that has known biological effects on humans or other animals.
- In pharmacology, a drug is a chemical substance used in the treatment, cure, prevention or diagnosis of disease or used to otherwise enhance physical or mental well-being.
- **Drug delivery** refers to approaches, formulations, technologies and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect.
- Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance.

History of drugs

- Drugs have long been used to improve health and extend lives.
- Wine was used at least from the time of the early Egyptians
- Narcotics from 4000 B.C.
- Medicinal use of marijuana has been dated to 2737 B.C. in China.
- In 19th century, active substances in drugs were extracted.
- Some of these newly discovered substances—morphine, laudanum, cocaine
- These were completely unregulated and prescribed freely by physicians for a wide variety of ailments.

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- During the American Civil War, morphine was used freely, and wounded veterans returned home with their kits of morphine and hypodermic needles.
- The modern medicines regulation started only after breakthrough progress in the 19th century life sciences, especially in chemistry, physiology and pharmacology
- This laid a solid foundation for the modern drug research and development and started to flourish after the second World War.
- The practice of drug delivery has changed dramatically in the last few decades
- Even greater changes are anticipated in the near future.



Current efforts in drug delivery

- Current efforts in the area of drug delivery include
 - the development of targeted delivery in which the drug is only active in the target area of the body (for example, in cancerous tissues)
 - sustained release formulations in which the drug is released over a period of time in a controlled manner from a formulation.
 - In order to achieve efficient targeted delivery, the designed system must avoid the host's defense mechanisms and circulate to its intended site of action

Some terms related to drug delivery

- **Pharmacokinetics**

- Pharmacokinetics or PK attempts to discover the fate of a drug from the moment that it is administered up to the point at which it is completely eliminated from the body
- What a body does to the drug is studied in PK

- **Pharmacodynamics**

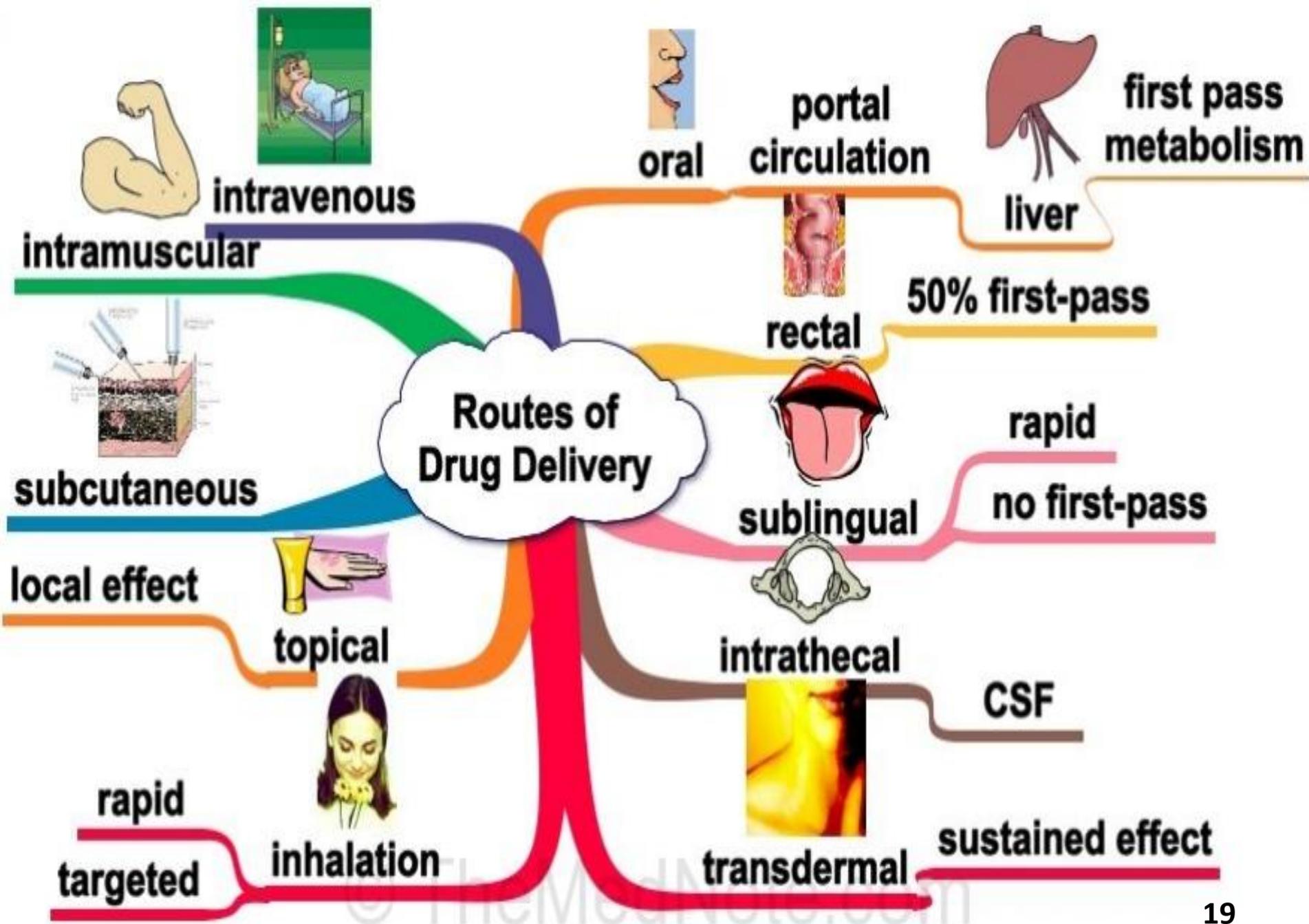
- Pharmacodynamics or PD is the study of the biochemical and physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect
- In other words, what the drug does to body is PD

Drug administration

- Administration is the delivery of a pharmaceutical drug to a patient
- There are three major categories of drug administration
 - **Enteral** – taking medication orally
 - **Parenteral** – introducing the medication directly to the circulatory system
 - **Others** – which includes introducing medication through intranasal, topical, inhalation and rectal means
- It can be performed in various dosage forms such as pills, tablets, capsules, injections or patches

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- The choice of route of administration for a drug should be based on factors that influence its systemic absorption
- This determines the rate of onset, peak effect and duration of action of the drug
- Changes in drug absorption rate may require adjustment in the dose or time interval between repeated drug doses.
- Drug absorption rate and route of drug administration depends on
 - The drug's water and lipid solubility
 - Blood flow to the site of absorption
 - The surface area available for absorption
 - Drug physico-chemical properties
 - Drug molecular size (molecular weight)
 - Half-life of drug
 - Chemical stability of drugs



Drug delivery routes

1. Oral

- Taken through the mouth
- As a liquid (syrup) or solid (capsules, tablets or chewable tablets)
- Absorbed through the intestines.
- Patient acceptance
- Most convenient and most often used
- Usually safest and least expensive

Disadvantages

- Poor uptake
- Chemical instability in GI tract
- Drug absorption takes time
- Some drugs can harm stomach lining



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2. Topical

- Applied on skin or mucous membrane
- Usually as a cream, lotion, gel or ointment.
- Act locally or systemically



3. Insufflation,

- Inhaled into the nose
- Blowing something (as a powder, gas or vapor) into body
- Mainly used for respiratory drugs



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4. Sublingual

- Placed under the tongue
- drug release in mouth followed by systemic uptake of the drug
- Being direct, it is faster

Disadvantages

- Eating, drinking affects absorption
- Not suitable for longer use
- Probability of swallowing and lose effect

5. Rectal

- As a suppository, that is absorbed by the rectal blood vessels.
- Faster onset and significantly less altered as it bypasses GI tract

Disadvantages

- Inconvenient
- Rectal absorption is unpredictable
- Some suppositories leak



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6. Transdermal

- Medicated adhesive patch on the skin
- Deliver a specific dose of medication through the skin and into the bloodstream
- Avoids drug food interactions, enzymatic activity and pH of GI tract
- Reduces daily dosing, thus, improving patient compliance
- Rapid termination of drug effect by removal of patch
- Suitability for self-administration

Disadvantages

- Drug must have some desirable physicochemical properties for penetration through stratum corneum
- Skin irritation or contact dermatitis can occur



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7. Inhalation

- Inhaled, as a solution, suspension or dry powder
- Deliver drugs to the lungs
- Lungs have large surface area and blood supply so rapid absorption of drug
- Used to treat pulmonary function or allergy symptoms

Disadvantage

- There is considerable variability in the absorption of drugs from the lungs so this route is not considered an alternative to intravenous administration.



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8. Injections or nano-needle array

- Many medications such as peptide and protein, antibody and gene based drugs, may not be delivered using these routes
- Because they might be susceptible to enzymatic degradation or can not be absorbed into the systemic circulation due to molecular size and charge issues
- For this reason these drugs have to be delivered by injection or a nano-needle array called the parenteral route.
- Administration by injection includes
 - Subcutaneous – in skin
 - Intramuscular – in muscle
 - Intravenous - in vein
 - Intrathecal – between vertebrae

Disadvantages

- Increased chance of infection
- Trained personnel required
- Needle sharing cause blood borne diseases
- People are scared of needle



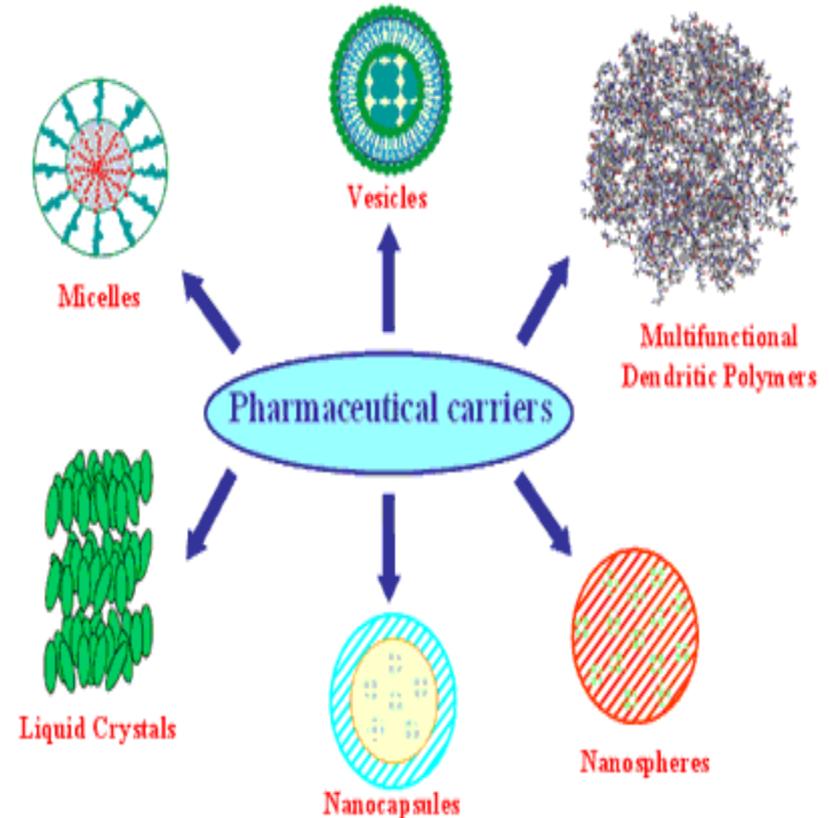
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9. Drug delivery carriers

- e.g. micelles, liposomes, vesicles, dendritic polymers and liquid crystals as well as nanocapsules are used as drug delivery carriers
- The carriers are
 - made to degrade slowly
 - stimuli reactive (pH or temperature sensitive)
 - Targeted

Disadvantages

- Production cost is high
- Leakage and fusion of encapsulated drugs
- Stability problem



Idea of microneedles

- Oral drug administration remains preferred method compared to injections
- But it is limited by
 - poor drug absorption
 - drug degradation
- Oral administration is not suitable for biologic class of drugs such as insulin, monoclonal antibodies and nucleic acids
- To replace injections and giving drugs through oral administration microneedle based technology was introduced



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- The likelihood of efficacy and safety of delivery across GI barrier with needles is supported by literature on ingestion of foreign objects.
- Surprisingly, the majority of foreign objects, including sharp objects, are capable of being passed via GI tract without complications
- Some previous studies (Butterworth *et al.*, 2004; Ikenberry *et al.*, 2011) and a large case series of 542 patients reporting the ingestion of foreign bodies noted that in those patients where surgery was required to remove foreign bodies, the size of objects was large, 3-16 cm that is well above the size range of needles used in ingestible device (Velitchkov *et al.*, 1996)
- This suggests that drug delivery may be possible from a capsule containing needles in a safe manner



History of microneedles

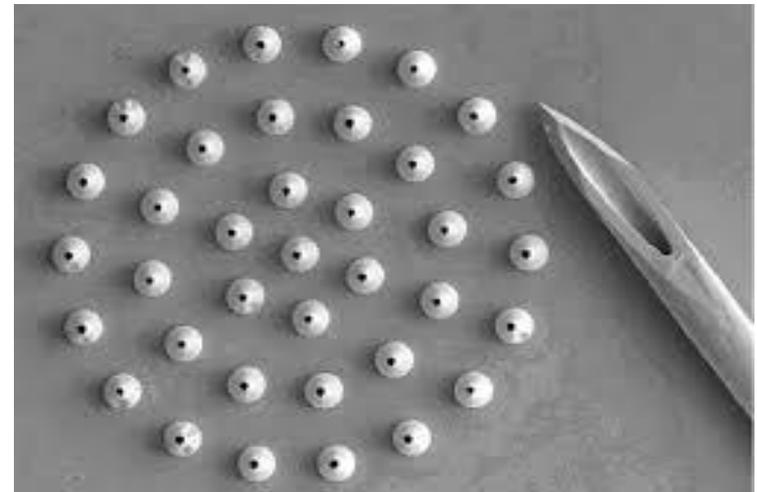
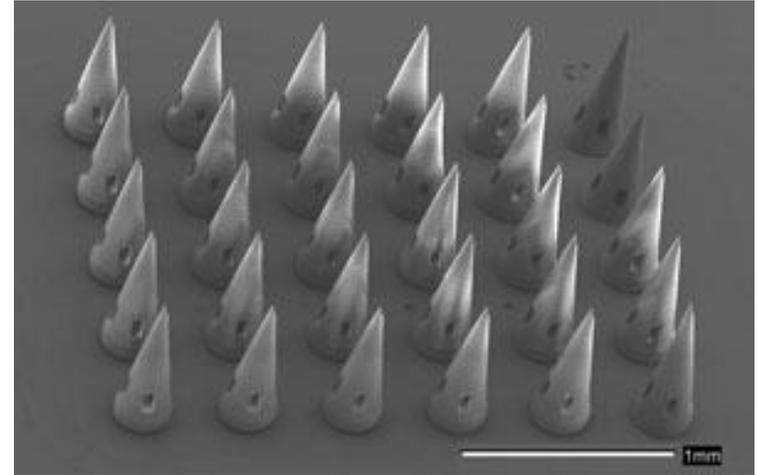
- ▶ Microneedles have been in development since the late 80s
- ▶ But became the subject of significant research starting in the mid-1990's
- ▶ Microneedle based technology has been extensively evaluated for transdermal drug and vaccine delivery to many parts of body like
 - i. solid microneedles for skin pretreatment to increase skin permeability
 - ii. microneedles coated with drug that dissolves off in the skin
 - iii. polymer microneedles that encapsulate drug and fully dissolve in the skin
 - iv. hollow microneedles for drug infusion into the skin.

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- ▶ Microneedles have been used to deliver a broad range of different low molecular weight drugs, biotherapeutics and vaccines, including a number of small-molecule and protein drugs and vaccines.
- ▶ Influenza vaccination using a hollow microneedle is in widespread clinical use
- ▶ Similarly, a number of solid microneedle products are sold for cosmetic purposes.
- ▶ Microneedles have also been adapted for delivery of bioactives into the eye and into cells
- ▶ Unlike the skin, the GI tract is insensible and provides unique opportunity for use of needle based delivery systems

Design of microneedle

- Microneedles are micron-scaled needles
 - so small that they are able to painlessly penetrate the skin.
- Current microneedle designs look like miniaturized beds of nails, fabricated from stainless steel or titanium
- Microneedles are available in either solid or hollow forms
 - Solid microneedles are dissolvable needles releasing the drug in skin
 - Hollow microneedles feature a narrow capillary through which therapeutic agents can be injected directly into the skin.

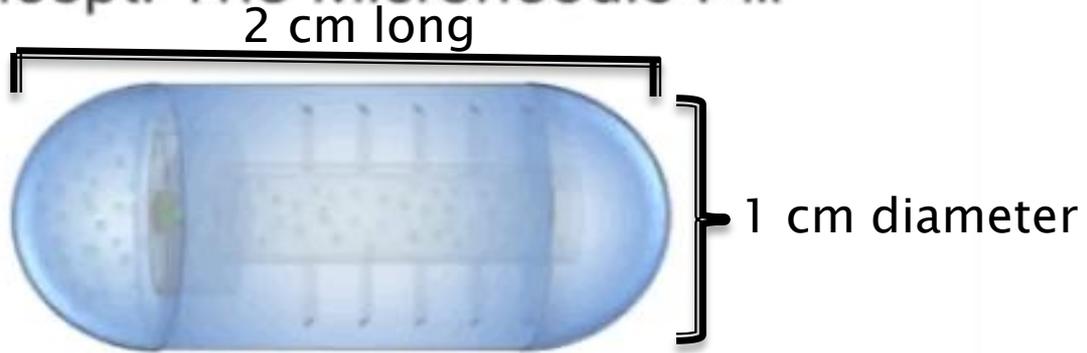


Microneedle capsule

- In an effort to design a capsule that is capable of delivering a wide range of drugs - while preventing degradation and effectively injecting the medicine into the GI tract
- Schoellhammer and colleagues from Massachusetts Institute of Technology (MIT) and Massachusetts General Hospital (MGH) constructed the capsule from acrylic, including a reservoir for the drug that is coated with hollow, 5 mm long needles made of stainless steel.
- The capsule measures 2 cm long and 1 cm in diameter.
- The capsule, coated with tiny needles, delivers medications painlessly to the GI tract.



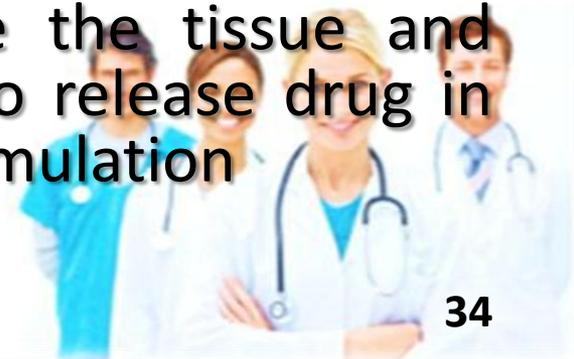
Concept: The Microneedle Pill



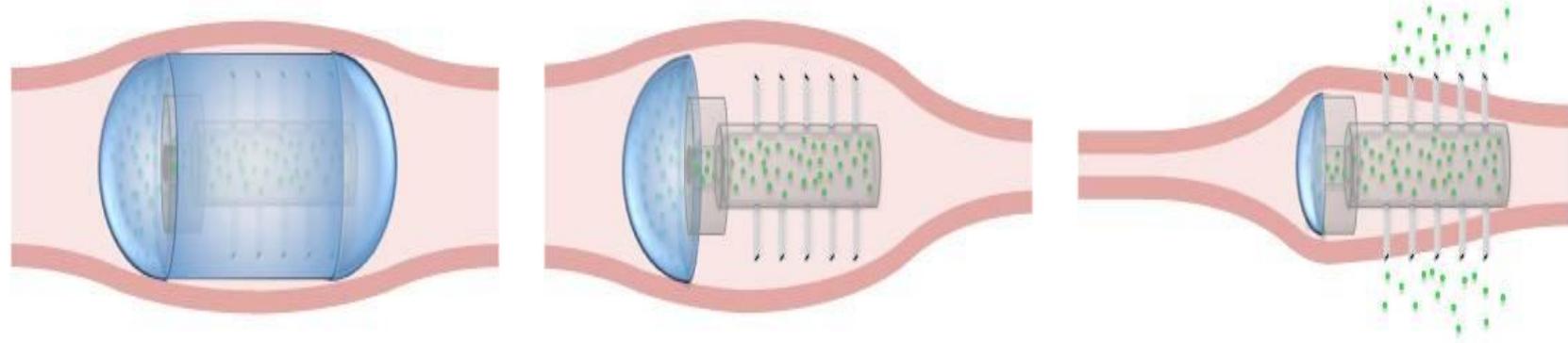
Therapeutic use concept of microneedle capsule

- Both hollow and solid microneedles could be used
- Microneedles are initially coated with pH responsive coating to aid in ingestion
- When pill reaches the desired location in GI tract, the coating dissolves revealing microneedles
- In **hollow microneedles**, the drug reservoir is compressed through peristalsis releasing drug through needles
- In **solid microneedles**, drug is formulated into microneedles. Microneedles penetrate the tissue and break off of the pill , leaving needle to release drug in controlled manner, based on needle formulation

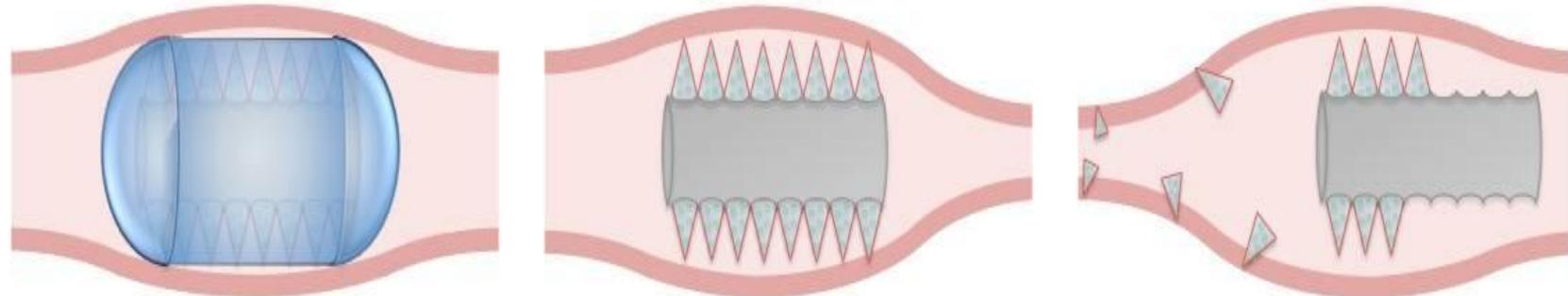
– Figure 4 from Traverso *et al.*, 2014



Hollow
Microneedles

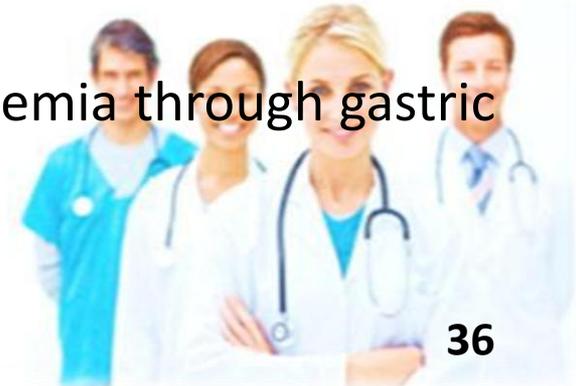


Solid
Microneedles



Gastric delivery is more efficient

- The ability for systemic delivery of insulin was evaluated by injecting the insulin in gastric, duodenal and colonic mucosa
- Insulin was chosen because
 - It has negligible oral bioavailability
 - It produces rapid physiologic response “hypoglycemia”(drop in blood glucose)
- 3 Yorkshire pigs (weighing 75-80 kg) were sedated and insulin injections were given in gastric, duodenal and colonic mucosa
- Then blood glucose levels were measured every two minutes by taking blood sample from catheter
- A subcutaneous injection of insulin was also given to compare hypoglycemic response with those of gastric, duodenal and colonic injections
- The results showed rapid induction of hypoglycemia through gastric absorption as compared to other routes
 - Table from Traverso *et al.*, 2014



Time in minutes to observe drop in blood glucose as a result of injection of insulin in various GI tissues and skin

Hypoglycemic onset time (min)

Skin	Stomach	Duodenum	Colon
23.08 _± 7.00	6.28 _± 4.48	6.66 _± 1.65	16.91 _± 6.39

Effective drug delivery through microneedles

- 3 Animals (pigs) were sedated and microneedle pill was endoscopically deployed in stomach
- Animals were monitored daily and radiographs were taken to track the pill movement
- Microneedles successfully injected insulin into the lining of the stomach, small intestine and colon
- Causing the animals' blood glucose levels to drop
- This reduction in blood glucose was faster and larger than the drop seen when the same amount of glucose was given by subcutaneous injection

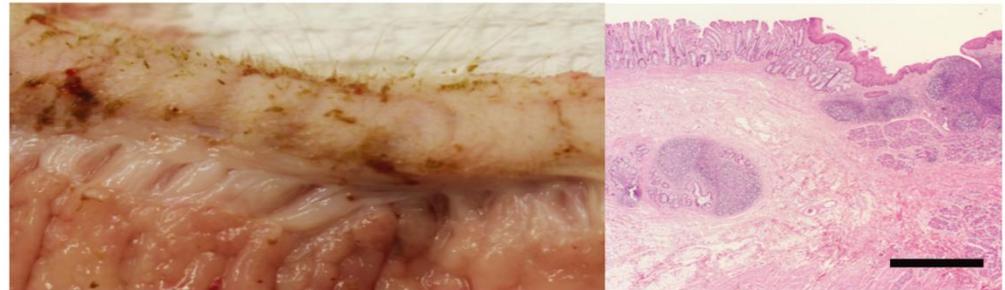
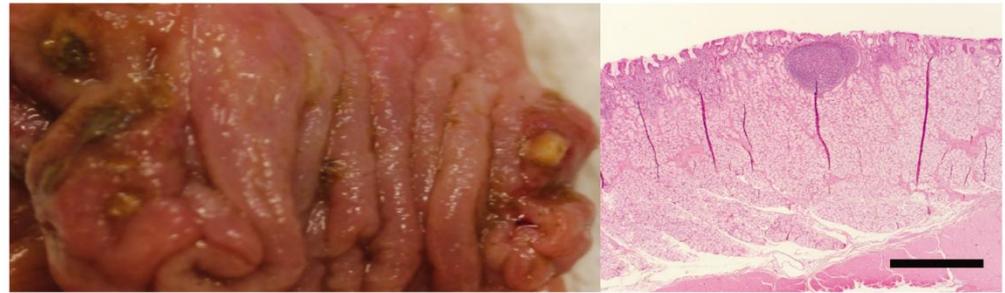
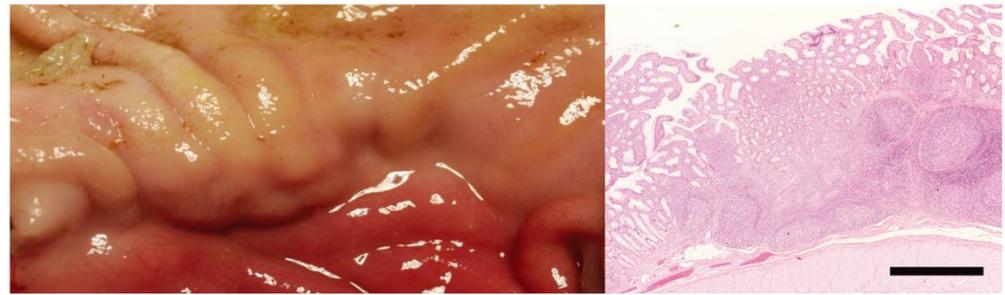
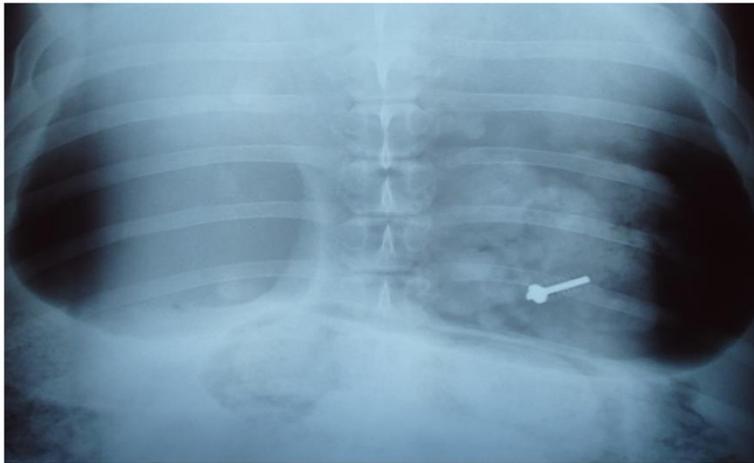


Safety assessment of microneedles

- The animals were euthanized and post-mortem inspection of entire GI tract confirmed passage of device
- Radiographs showed no intestinal obstruction or perforation
- GI tissue was evaluated and found to be macroscopically normal
- Histological examination was also done and appeared normal
- It took more than a week for capsules to move through the entire digestive tract

– Figure 3 from Traverso *et al.*, 2014

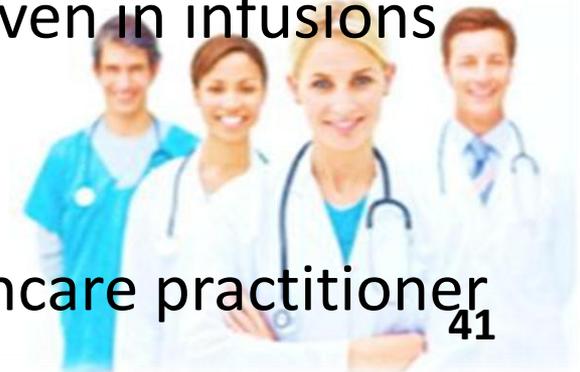




- a) Endoscopic deployment of microneedle capsule in pig stomach
b) X-ray showing progression of capsule
c), d), e) Gross and histological image of pylorus, ileocecal valve and anal canal after natural passage of capsule

Advantages of microneedle

- Suitable for macromolecules and biologics delivery
- Use of microneedles is completely painless as GI tract has no pain receptors
- Bypassing the harsh GI mucosal environment
- Drug kinetics are much better and much faster onset
- For diabetics it could mean no more insulin injections
- For those with rheumatoid arthritis, Crohn's disease or ulcerative colitis, it could mean a new way to receive biological therapies that are currently given in infusions
- High patient compliance
- Elimination of needle-stick injuries
- Removal of the need for a trained healthcare practitioner



Avenues of exploration

- The safety and natural passage of such a device are paramount to further investigation
- Evaluation of drug release kinetics and kinetics of clearance of device using varying microneedle geometrics will be required
- Geometry and design of microneedles would be interesting area for their effect on retention time of capsule
- Solid, drug-containing microneedles could be fabricated from biocompatible polymers
- Peristaltic motion in the GI tract could be utilized to compress the capsule

Inference

- By demonstrating the potential safety and efficacy of this method, this study provides the basis for further development of integrated microneedle devices for oral macromolecule delivery



Reference

- Traverso, G., C. M. Schoellhammer, A. Schroeder, R. Maa, G. Y. Lauwers, B. E. Polat, D. G. Anderson, D. Blankschtein and R. Langer. 2014. Microneedles for drug delivery via gastrointestinal tract. Journal of pharmaceutical sciences. 1-6.