# Nanomedicine for the Route of Administration (RoA): L3 Oral L4 Pareneteral

David Clarke

Professor of Drug Delivery, University of Manchester, UK

**Lecture Series at the**

**Institute of Chemical Biology & Fundamental Medicine for Siberian Branch of Russian Academy of Sciences**



## L3: Nanomedicine for the route of administration (RoA)

**Intended learning outcomes:**

- To understand different epithelia in terms of the physical, chemical and biological barriers to drug delivery
- To apply this understanding at the nano-scale to see how nanoparticles improve drug delivery at the main routes of administration (RoA):
  - oral → intestine (gut)
  - patches → skin
  - inhalers → lung

  For large and small molecule drugs:
- To introduce L4: 'Overcoming biological barriers ...'

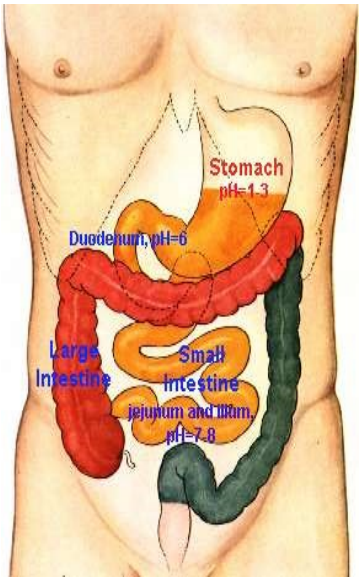
# L3: Oral → intestines

**Stomach:**

- Very acidic pH 1 → 3
- low surface area for drug absorption
- emptying delayed by food, but empties often without food

**Small intestine:**

- neutral pH, enzymes destroy biologicals
- very high surface area and excellent blood supply for absorption into body
- but absorption into blood suffers (1st pass) metabolism in liver
- bile acids (cholate surfactants) disperse lipids to absorb into intestine lymphatic system, which avoids metabolism in liver




## Biopharmaceutics Classification System (BCS) & Regulation - Biowaiver eligibility

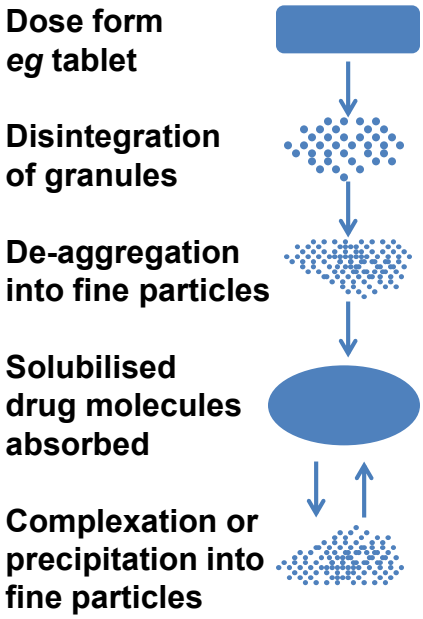
Reliability of predicting bioavailability from dissolution studies

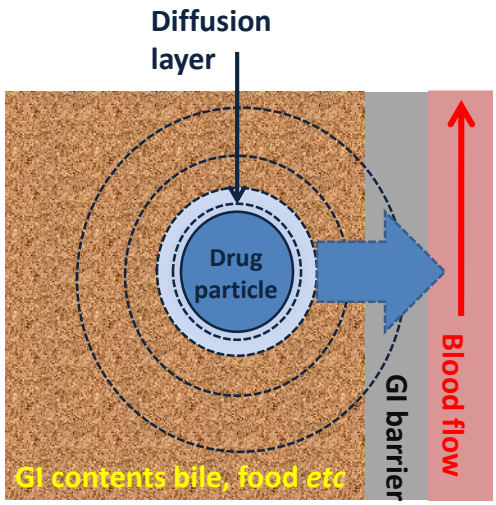
| | High solubility | Low Solubility |
|---|---|---|
| High permeability | **Class I**<br>High solubility<br>High permeability<br>**Eligible for Biowaiver** | **Class II**<br>Low solubility<br>High permeability<br>**Eligible for Biowaiver only if weak acids, highly soluble at pH6.8, plus dissolution** |
| Low Permeability | **Class III**<br>High solubility<br>Low permeability<br>**Eligible for Biowaiver if very rapidly dissolving** | **Class IV**<br>Low solubility<br>Low permeability<br>**Not eligible for Biowaiver** |

Highly soluble when largest dose is soluble in <250mL water over pH from 1.0 to 7.5

Highly permeable when >90% absorption of the administered dose

# Dissolution of Dose Forms




Soluble & permeable fraction rapidly absorbed as sink conditions (steep diffusion gradient) into blood

## Permeation, log P, pH & log D

pH partition absorption of ionised drugs depends on dissociation constant ($K_a$ or $pK_a$) & partition coefficient (P or LogP):

Distribution coefficient (D) is the 'effective' partition coefficient, accounting for the degree of ionisation:

weak acids: $D = [HA_{org}] / \{ [HA_{aq}] + [A^-_{aq}] \}$

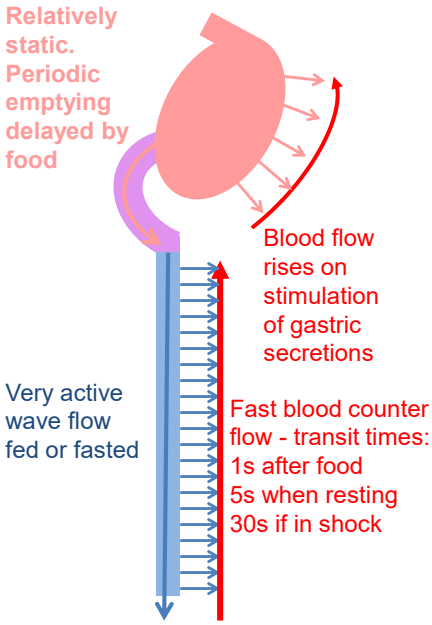
weak bases: $D = [B_{org}] / \{ [B_{aq}] + [BH^+_{aq}] \}$

- D depends on pH and is related to P for a weakly basic drug:

  $\text{Log } D = \log P - \log \{1 + \text{antilog } (pK_a - pH) \}$

  D can be approximated at any pH using the $pK_a$ of the drug.
- Many limitations *eg* not stirred – convective flow, ionised may also be absorbed, different (lower) pH at membrane surface, secretions, disruption of lipid membrane (*eg* surfactants, QACs) AND BIOLOGICAL TRANSPORT – see L4.

# Revision: weakly basic drug generalisations



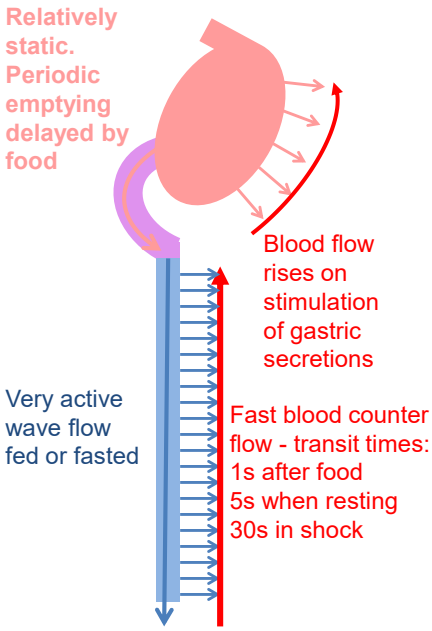

**$RNH_2 + H^+ \rightarrow RNH_3^+$**
Food increases time for dissolution, acidity increases % protonated (charged) base and solubility of drug. Charged (protonated) base less lipophilic & less permeable.

**$RNH_3^+ \rightarrow RNH_2 + H^+$**
Emptying into increased pH reduces % protonated base and solubility, precipitate particles may form

Uncharged base more lipophilic & permeable

Rapid blood flow maintains high diffusion gradient from particles

# Revision: weakly acidic drug generalisations

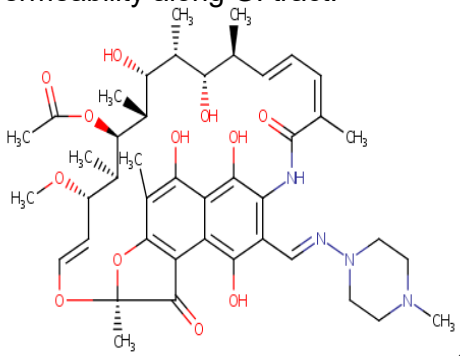



**$RCOO^- + H^+ \rightarrow RCOOH$ (HA)**
Food increases time for dissolution, acidity increases % uncharged (non-ionised) acid.
More lipophilic & permeable, but decreases solubility, precipitate particles may form. Less surface area.

**$RCOOH \rightarrow RCOO^- + H^+$**
Emptying into increased pH reduces % uncharged acid, increases % ionised and solubility.
Charged (ionised) acid less lipophilic & lower partition into lipid.
Rapid blood flow maintains high diffusion gradient for solubilised & permeable fraction of drug.

# Case Study: Rifampicin

One of oldest effective TB treatments, but major issue with variable oral bioavailability.
MW 823 Da & LogP 4.2 (un-ionized) with a weak acid ($pK_a$ 6.9) & a weak base ($pK_a$ ~8) affecting solubility & permeability along GI tract.



| pH | Solubility mg/ml | Log D | Permeability cm/s |
|---|---|---|---|
| 1.4 | 125.5 | -1.27 | Stomach |
| 2.4 | 11.4 | -0.23 | 0.02 |
| 3 | 1.15 | 0.76 | |
| 3.5 | 0.75 | 0.95 | |
| 4 | 0.99 | 0.83 | Duodenum |
| 4.5 | 1.25 | 0.73 | 0.62 |
| 5.2 | 1.53 | 0.64 | |
| 6 | 1.65 | 0.61 | Jejunum |
| 6.8 | 2.54 | 0.42 | 0.24 |
| 7.4 | 3.35 | 0.3 | 0.4 Illeum |
| 8 | 5.44 | 0.09 | 0.12 Colon |

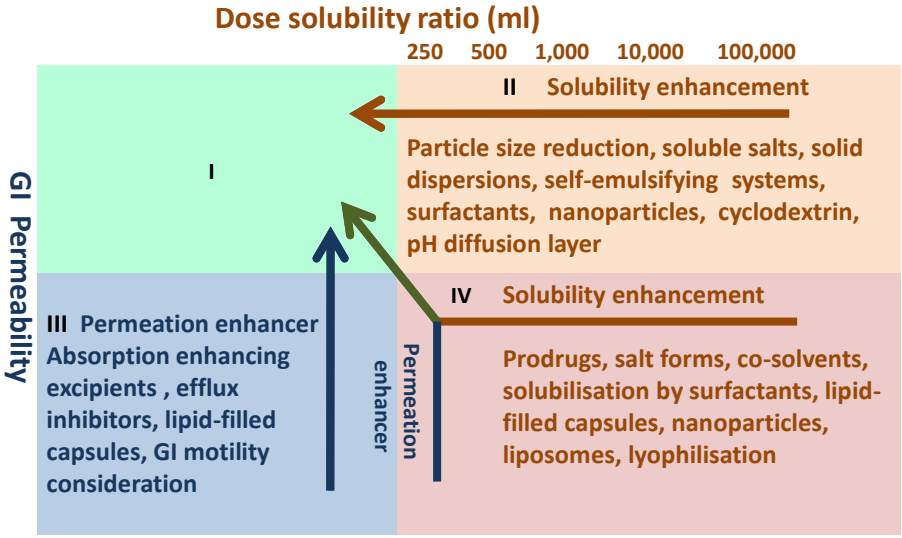


# Major issues with poor drug solubility

40% of new (small molecule) drugs are poorly soluble or lipophilic compounds (combinatorial chemistry and high throughput screening over the last 2 decades):

- Poor bioavailability→ Sub-optimal dosing
- Food effects: fed/fasted variation in bioavailability
- Lack of dose-response proportionality
- Harsh excipients *eg* excessive use of co-solvents
- Use of extreme basic or acidic conditions to enhance solubilisation
- Uncontrollable precipitation after dosing
- Patient non-compliance - inconvenience of the dose form

# Summary of approaches to shift solubility-dissolution & permeation characteristics




# Nanoparticle engineering

Reducing particle size is important in solubilisation:

**a) increases surface area (A)**

$dm / dt = k (C_s - C)$

where the rate constant $k$ = DA / h (Noyes Whitney)

*eg* 5 μm → 120 nm increases A by 41.5 X

**b) reduces diffusion layer thickness (h)**

**c) increases saturation solubility (S )**

$S = S_o \exp (2 \chi M / r \rho RT)$ *eg* >10-15% increase on reduction to 100 nm diameter

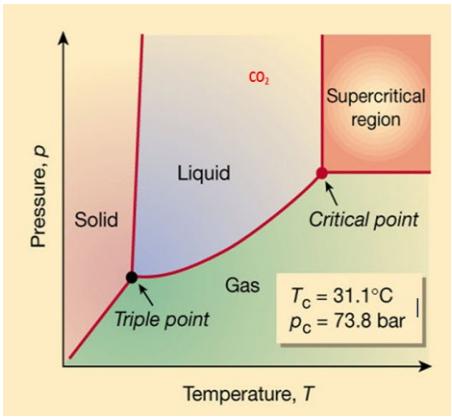
where $\chi$ crystal interfacial tension, M molecular weight, r particle radius, $\rho$ density

# Supercritical fluids (SCFs *eg* $CO_2$)

SCFs assume the properties of both a liquid and a gas: highly compressible, allowing small changes in P or T to greatly alter their density, mass transport and solvating power

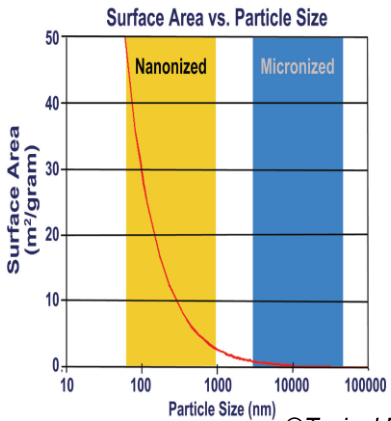
SCF-solubilisation of drugs

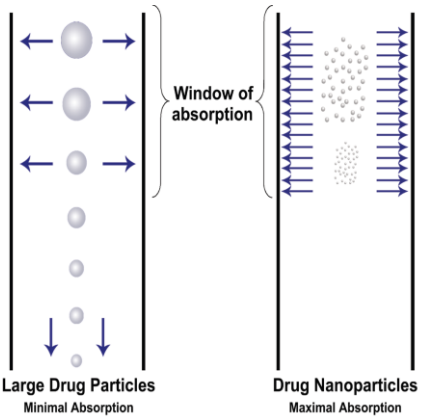
- avoids toxic organic solvents
- makes small particle sizes possible
- 5 - 2,000 nm in diameter




# Surface area *v.* particle size & improved absorption

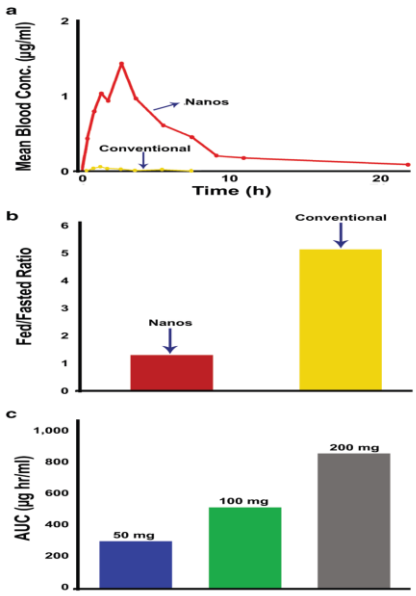
Higher absorption in small intestine because of higher surface to mass ratio of small particle suspension, and greater dissolution in the transit time through the small intestine – window of absorption




©*Toxicol Pathol 2008 36: 43*

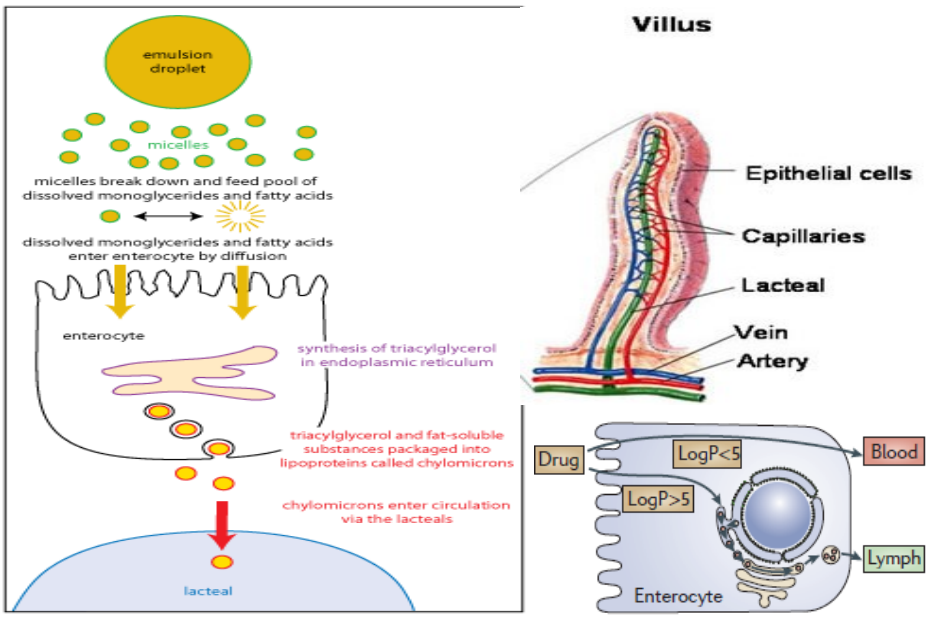
# Benefits of nanoparticles




©Toxicol Pathol 2008 36: 43

- Greater bioavailability: higher $C_{max}$, AUC
- Less variability with food: smaller difference between fed and fasted bioavailability
- Dose proportionality: AUC proportional to dose

# Lymphatic absorption of lipids/fats



# Lipid-based formulations

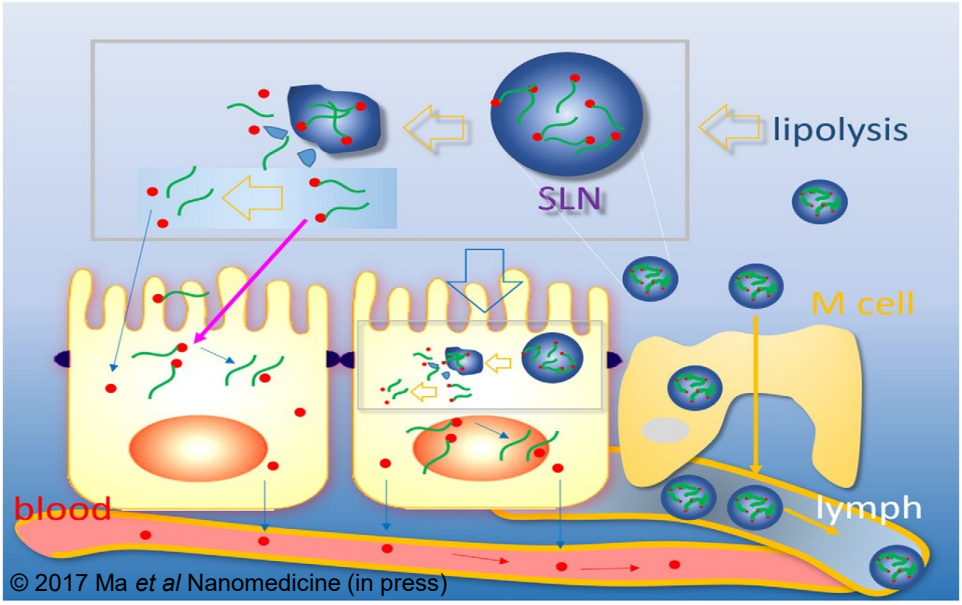
Lipid in the duodenum (<2g ~ 2 capsules or food) stimulates secretion of biliary lipids (cholate surfactants), generating colloidal micelles, mixed micelles, vesicles & emulsion droplets.

- Digestion of lipids is an important step for the bioavailability enhancement of lipid solutions:
- Solubilising and absorption effect from reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract
- Absorption into the intestinal lymphatics (lacteals) and then into the systemic circulation, avoiding first-pass metabolism in the liver

## Lipid formulation classification (Poulton)

| | Type I | Type II | Type III A | Type III B | Type IV |
|---|---|---|---|---|---|
| | | **SEDDS** | **SMEDDS** | | **SNEDDS** |
| Triglycerides | 100% | 40-80% | 40-80% | <20% | |
| Water insoluble surfactants HLB <12 | | 20-60% | | | 0-20% |
| Water-soluble surfactants HLB>12 | | | 20-40% | 20-50% | 30-80% |
| Hydrophilic co-solvents | | | 0-40% | 20-50% | 0-50% |
| **Particle size** | **Coarse** | **>100 nm** | **<100nm** | **50-100nm** | **<50nm** |
| Aqueous dilution | Limited | Unaffected | Some loss | Phase changes | Phase changes |
| Digestibility | Crucial | Not crucial, but likely | Not crucial, but may inhibit | **Not required** | **Not required** |

# Lipid nanoparticle absorption



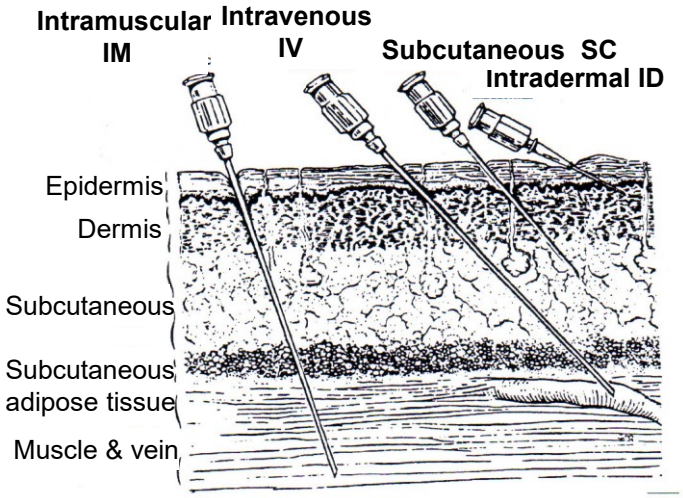

# L4: Parenteral Routes of Admin (RoAs)

- One third oral → GI tract (gut)
- Two thirds parenteral routes of administration (RoA)
- Growth in parenteral:
  - avoid problems of GI tract
  - device control of delivery
  - nanomedicines
  - biologics

Parenteral is derived from Greek *para enteron* - avoid intestines – any route other than into mouth / GI tract

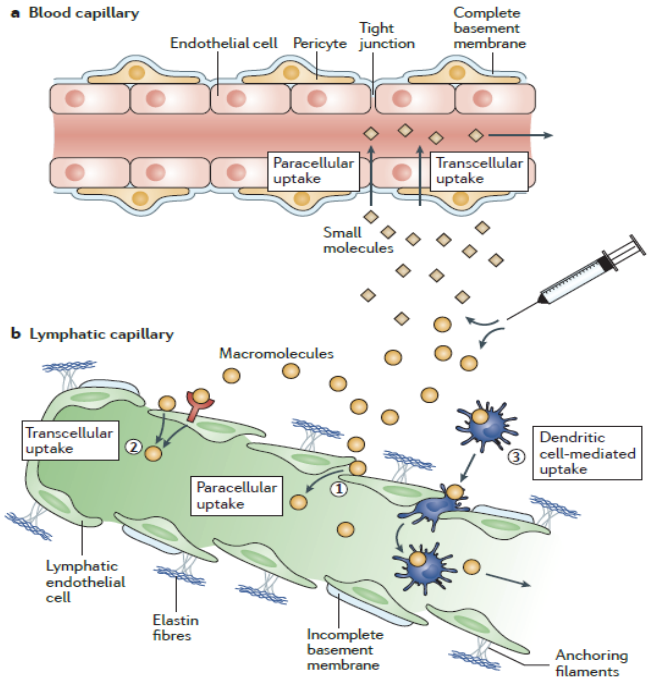
| RoA | Share % |
|---|---|
| Oral | 32 |
| Pulmonary | 27 |
| Nasal | 11 |
| Injection | 9 |
| Transdermal | 8 |
| Other | 13 |

# Needles (percutaneous)




**IV**
- veins in hands, arms, legs or feet
- catheter for long term often with heparin lock to prevent clotting

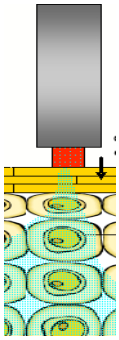
**IM, SC, ID** routes more limited on volume and hypertonic formulations generally avoided.




© 2015 Nature Rev Drug Discovery 14: 786

- Blood capillaries have tight junctions - small molecules pass
- Lymphatic capillaries have wide junctions – large & small molecules pass

# Painless & needle-free injectors



Re-usable & needle-free injectors:

- some spring-powered with thousands of uses, others use high pressure gas to force drug through skin
- subcutaneous, intradermal or intramuscular administration bioequivalent with regular needle injection

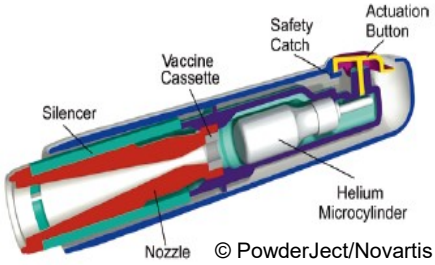
Many examples - a few below:

© IntraJect (Aradigm) © MiniJect (BioValve) © PenJet Corp

# PowderJect (Novartis) injector

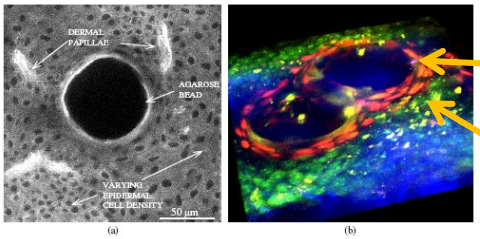
Gas burst acceleration of drug particles to super-sonic speeds:

- Gas bursts drug cassette (0.5-5 mg)
- burst shock front passes down nozzle, carrying particles
- Supersonic Mach 2-2.5 →1.5 @exit
- highly potent drugs & vaccines



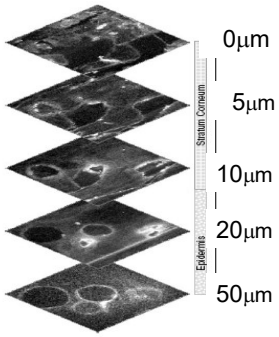

© PowderJect/Novartis

Particles shot thru skin to epidermis & dendritic cells (vaccine - antigen presenting cells)




Damaged cells (red)

Viable cells (green)



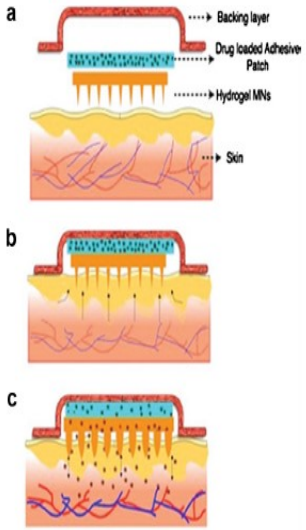
# Microneedle patches

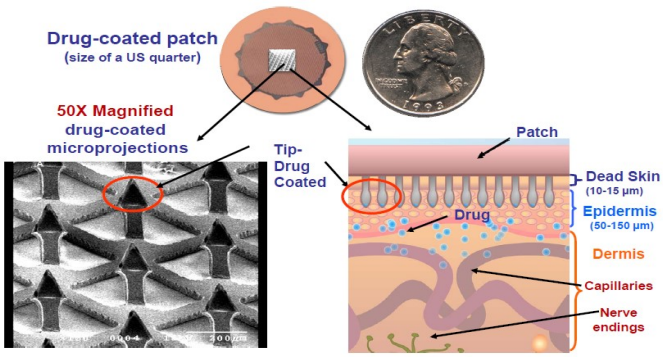
Skin pierced with short needles to deliver drugs in a minimally-invasive manner - for small molecules, proteins and nanoparticles from extended-release patches:

(i) increase skin permeability by creating micron-size pathways in skin,

(ii) actively drive drugs into the skin during microneedle insertion,

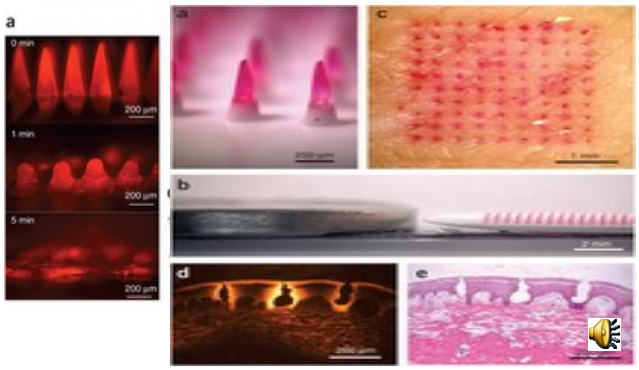
(iii) microneedles pierce thru dead skin (stratum corneum), across the epidermis & into the superficial dermis too.



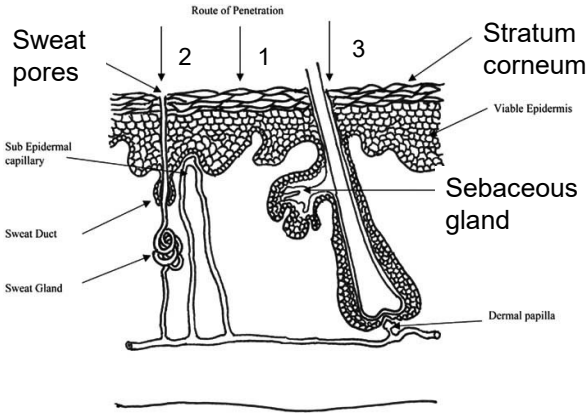




Drug-coated microneedles

Dissolving microneedles encapsulating drug



# Transdermal penetration routes




1. Directly across the stratum corneum

Shunt or appendageal routes:

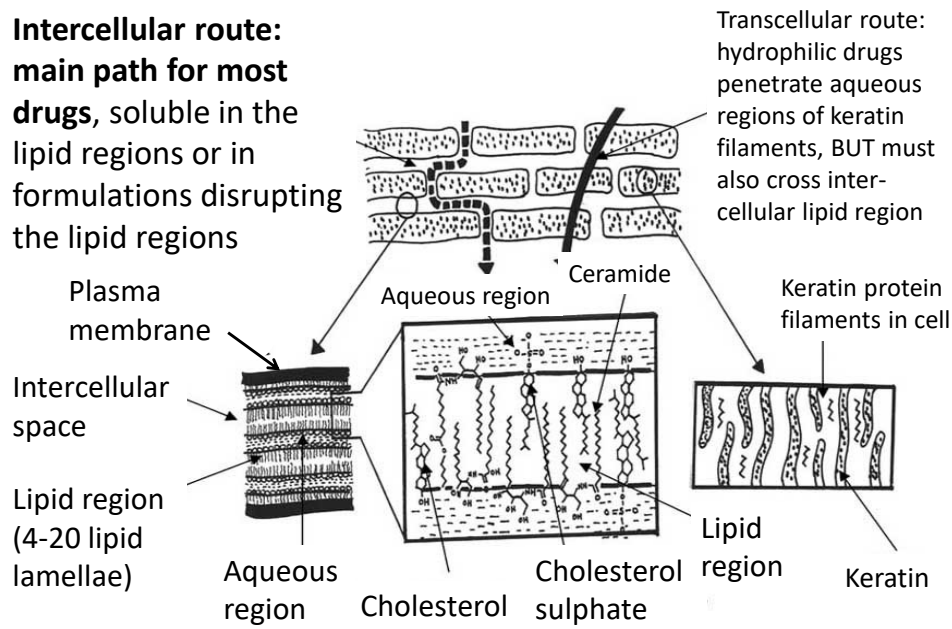
2. through the sweat ducts,
3. *via* the hair follicles and sebaceous glands

Skin penetration enhancement focused on increasing transport across the stratum corneum.

Appendages small area for permeation (~ 0.1% area), small contribution except: iontophoretic drug delivery primarily *via* the shunt routes as less electrical resistance.

# Inter-cellular >> transcellular penetration

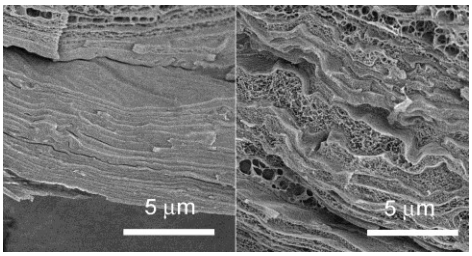
**Intercellular route: main path for most drugs**, soluble in the lipid regions or in formulations disrupting the lipid regions



# SC modification: hydration

Water widely used & safe to increase skin penetration of hydrophilic and lipophilic permeants:

- alters drug solubility & partitioning
- hydration swells and opens SC structure → increased penetration.



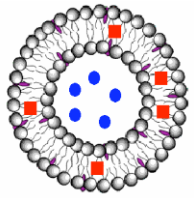

Water content ~15 - 20% of dry weight, but hydration varies:

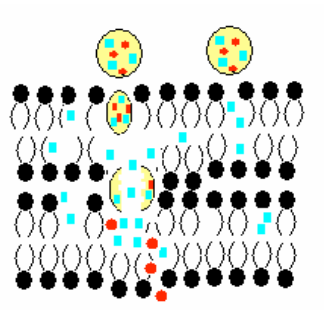
- occlusion with transdermal patches, plastic films, paraffins, oils, waxes as components of ointments and water-in-oil emulsions that prevent water loss from skin
- oil-in-water emulsions that donate water into skin.

# SC modification: liposomes & lipid particles

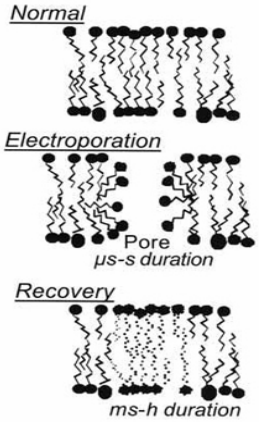
Liposomes hydrate and alter lipid layers, especially where lipids similar to stratum corneum lipids

- **Deformable liposomes** or transfersomes: 10-25% surfactant with 3-10% ethanol, act as "edge activators", conferring deformability, allowing them to squeeze through channels less than one-tenth their diameter.





# Powered patches - electroporation




Short, high-voltage pulses reversibly disrupt lipid lamellae of strateum corneum (SC):

electric field initially concentrated in SC (higher resistance than deeper layers).

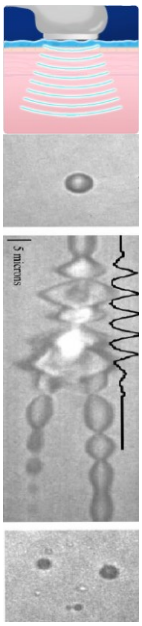
As SC made permeable, resistance drops, electric field distributes into the deeper tissues, with sensory & motor neurons

Pain & muscle stimulation avoided by using closely-spaced microelectrodes that constrain the electric field to within the SC.
Electroporation used with microneedle patches.
Electro-pores persist for hours, increasing diffusion by orders of magnitude for drugs, peptides, proteins & nucleic acids.

# Powered patches - phonophoresis

Ultrasound is an oscillating pressure wave at a frequency too high for humans to hear.

- Increases permeability to small, lipophilic compounds
- Dominant effect disrupts stratum corneum lipid lamellae structure
- Formation, oscillation and collapse of bubbles in an ultrasonic pressure field increases delivery




Pulsed lasers similarly used to increase skin permeability by a related shockwave mechanism.

# Lung RoA: benefits of inhaling drugs

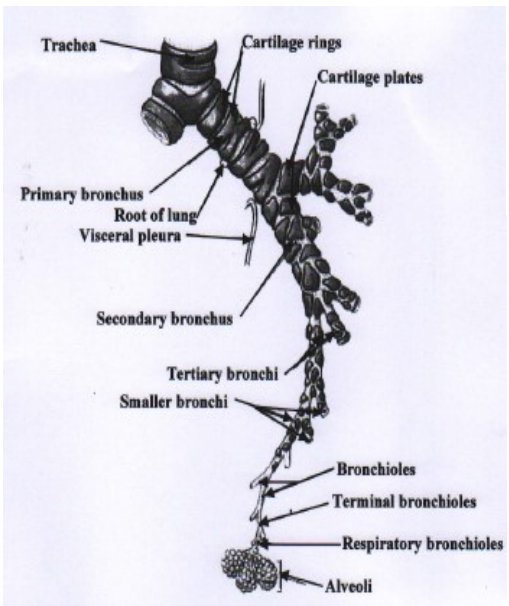
Local treatment (*eg* asthma, lung diseases)

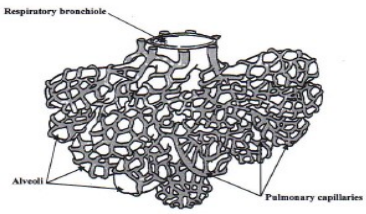
- Rapid onset of action
- Avoids drug degradation in gut
- Avoids 1st pass metabolism
- Low dose avoids toxicity
- Controls dose
- Small volume
- Container protects drug

Systemic RoA into blood:

- Avoids drug interactions
- Avoids variable pharmacokinetics of oral administration
- Acute pain *eg* fentanyl, morphine
- Fragile drugs: biologics *eg* rapid-acting insulin, calcitonin for osteoporosis *etc*

# Lung airways branch: bronchi to alveoli

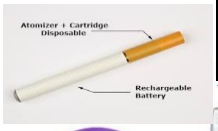



- Each lung 300 million alveoli, 70 $m^2$ surface area
- Lungs have 2 and 3 lobes, approx 140 $m^2$ surface area
- 9-10 breaths per minute
- 4-5 litres per minute blood
- Branched (fractal) airways modelled as 23 branches

# Inhaler devices

1. **Sprays** - useful for upper respiratory tract
2. **Pressurized metered dose inhalers (pMDIs)** - solvent propellants
3. **Super fine particle inhalers** for small airways disease (SAD)
4. **Nebulisers**: drug in polar solvent usually water
5. **Dry powder inhalers (DPIs)**
   - no solvent propellant
   - dry powder fluidises when patient inhales

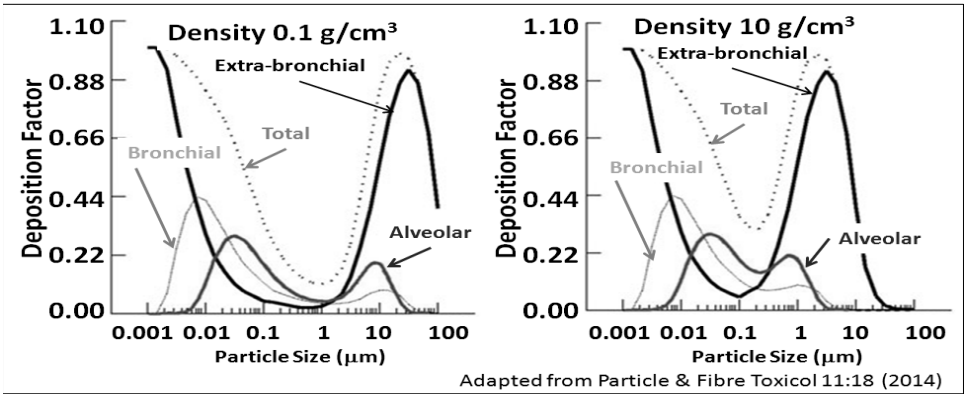


# Why & where do particles deposit?

- Inertial impaction & gravitational sedimentation:

$$\text{Aerodynamic diameter} = \text{Geometric diameter} \times \left[\frac{\text{Density}}{\text{Shape}}\right]^{\frac{1}{2}}$$

- Diffusion (nanoparticle sizes only)




Adapted from Particle & Fibre Toxicol 11:18 (2014)

# Case study: small airways disease

Child model (baboon ape), images of deposition of 3 different aerodynamic diameter (AMAD) particles

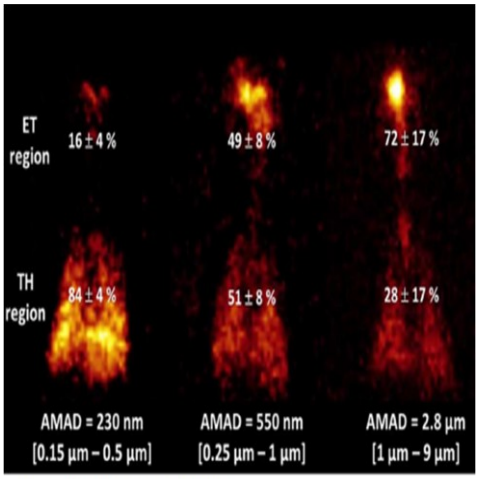
ET - extrathoraxic regions

TH - thoraxic

Colour from:

yellow/lighter image (high deposition) to

brown/darker image (low deposition).






# Nanoparticles for RoA

- Oral:
  - NPs increase surface area and drug solubilisation
  - lipid NPs absorb *via* lymphatic pathway
- Skin - penetrate dead skin layer:
  - painless injectors
  - microneedle , ultrasound & electroporation patches
  - lipid NPs / liposomes fluidize lipid lamellae
- Lung:
  - increase deposition in alveolae (avoids upper airways)
  - systemic absorption into blood

L6 & 7: barrier penetration (epithelia & endothelia)