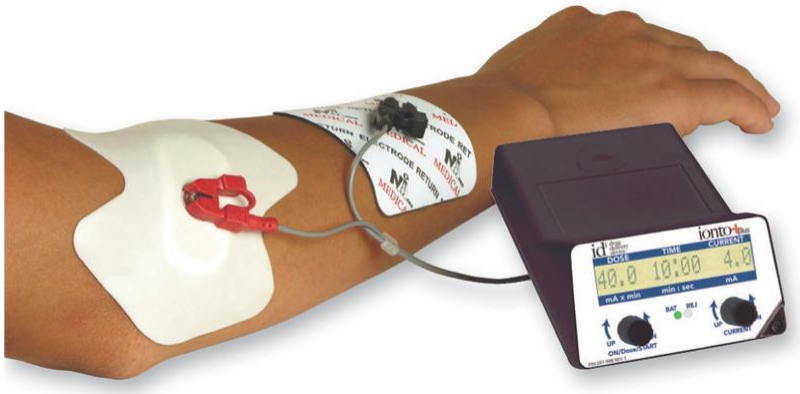
Iontophoresis



Iontophoreis

- Introduction of ions into the body using direct electrical current
- Transports ions across a membrane or into a tissue
- It is a painless, sterile, noninvasive technique
- Demonstrated to have a positive effect on the healing process

Iontophoresis vs Phonophoresis (sonophoresis)

- Both techniques deliver chemicals to biologic tissues
- Phonophoresis uses acoustic energy (ultrasound) to drive *molecules* into tissues
- Iontophoresis uses electrical current to transport *ions* into tissues

3

Pharmacokinetics of Ion Transfer

- Iontophoresis delivers medication at a constant rate so that the effective plasma concentration remains within a *therapeutic window* for an extended period of time
  - ♦ Therapeutic window – range between the minimum plasma concentration of a drug necessary for a therapeutic effect and the maximum effective plasma concentration (above which adverse effects may occur)

4

Pharmacokinetics of Ion Transfer

- Iontophoresis facilitates the delivery of charged and high molecular weight compounds through the skin
  - Overcomes the resistive properties of the skin
- Iontophoresis decreases absorption lag time while increasing delivery rate
  - Much better than passive skin application
- Iontophoresis reduces the development of tolerance to drug
  - Does so by providing both a spiked and sustained release of the drug

5

Pharmacokinetics of Ion Transfer

- Rate at which a medication may be delivered is determined by:
  1. The concentration of the ion
  2. The pH of the solution
  3. Molecular size of the solute
  4. Current density
  5. Duration of the treatment

6

Pharmacokinetics of Ion Transfer

- Mechanisms of drug absorption via iontophoresis is similar to the administration of drugs via other methods
- Advantages of taking medication via iontophoresis relative to oral medications
  - ♦ Concentrated in a specific area
  - ♦ Does not have to be absorbed within the GI tract
  - ♦ Safer than administering a drug via injection

7

Movement of Ions In Solution

- Ionization - soluble compounds (acids, alkaloids, salts) dissolve into ions that are suspended in solutions
- Resulting solutions are called *electrolytes*
- Electrophoresis - movement of ions in electrolyte solutions according to the electrically charged currents acting on them

8

Movement of Ions In Solution

- Cathode
- Highest concentration of electrons in tissues
  - Repels positively charged ions
  - Attracts negatively charged ions
  - Accumulation of negatively charged ions in a small area creates an *acidic* reaction

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Movement of Ions In Solution

- Anode
  - Lower concentration of electrons in tissues
  - Repels negatively charged ions
  - Attracts positively charged ions
  - Accumulation of positively charged ions in a small area creates an alkaline reaction

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Movement of Ions In Solution

- With iontophoresis…
  - Positively charged ions are driven into tissues from positive pole
  - Negatively charged ions are driven into tissues from negative pole
- The pole that is driving ions into tissue is called the *active electrode*
  - The other pole is called the inactive electrode
- Knowing correct ion polarity is essential to administering an effective iontophoresis treatment

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Movement of Ions In Tissue

- Force which acts to move ions through the tissues is determined by…

1. Strength of the electrical field
2. Electrical impedance of tissues
   - ♦ Skin and fat = high impedance*, poor conductors
   - ♦ Sweat glands = low impedance; therefore, sweat ducts is the primary path by which ions move through the skin

* Skin impedance decreases during an iontophoresis treatment due to increased blood flow between the electrodes

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Movement of Ions In Tissue

- Strength of the electrical field is determined by the *current density*
- ♦ Difference in current density between the active and inactive electrodes establishes a gradient of potential difference
  - ♦ Produces ion migration within the electrical field
  - ♦ Ions move according to their electrochemical gradient

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Movement of Ions In Tissue

- Current density may be altered by…
- ♦ 1). Increasing or decreasing current intensity
  - – Higher current intensity is necessary in areas where skin and fat layers are thick
  - – Increases risk of burns around negative electrode
- ♦ 2). Changing the size of the electrode
  - – Increasing the size of the electrode will decrease *current density* under that electrode
  - – Negative pole pad should be larger (2x) because an alkaline reaction (+ ions) is more likely to produce tissue damage than an acidic reaction (- ions)

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Movement of Ions In Tissue

- The quantity of ions transferred into the tissues via iontophoresis is **directly** proportional to…
- ♦ 1). Current density at the active electrode
- ♦ 2). Duration of the current flow
- ♦ 3). Concentration of ions in solution

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Movement of Ions In Tissue

- Once the medication (ions) passes through the skin, the ions recombine with existing ions and free radicals in the blood
  - Increased blood flow between electrodes
- Form new compounds necessary for favorable therapeutic effects

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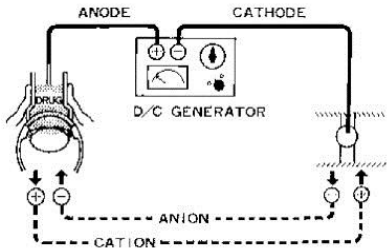
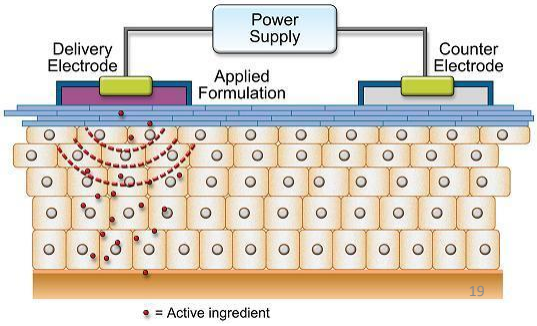
Iontophoresis Techniques

Iontophoretic devices

- Basic components:

1. A power source – battery or on-line unit with voltage regulator
2. A miliampere meter to measure current
3. Rheostat – controls the amount of current flowing through the system
4. 2 electrodes
   - Mostly platinum – releases almost no ions, undergoes degradation at slow rate and is non-toxic





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Iontophoresis Generators

- Produce continuous DC
- Assures unidirectional flow of ions

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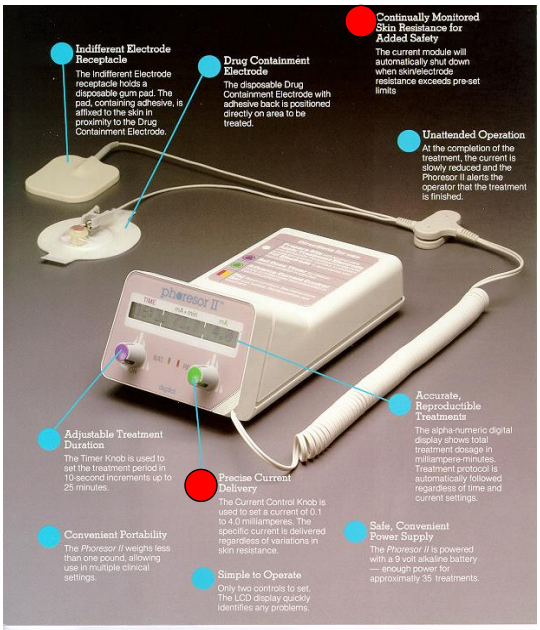
Iontophoresis Generator

- Intensity: 3 to 5 mA
- Unit adjusts to normal variations in tissue impedance
  - Reduces the likelihood of burns
- Automatic shutdown



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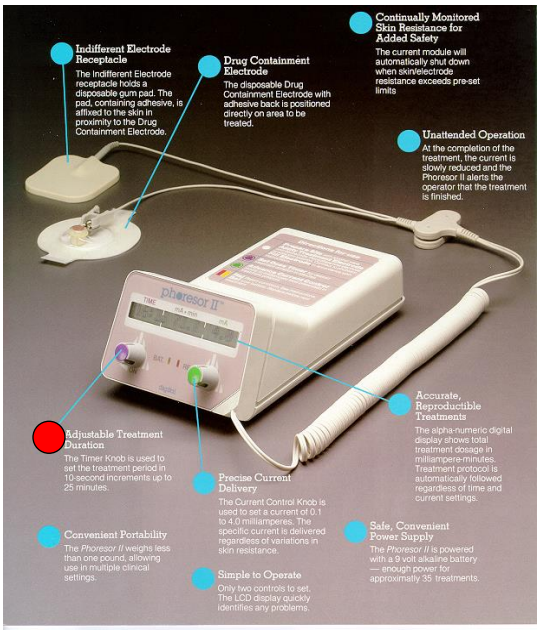
Iontophoresis Generator

- Adjustable Timer
  - Up to 25 min



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Current Intensity

- Low amperage currents appear to be more effective as a driving force than currents with higher intensities
  - Higher intensity currents tend to reduce effective penetration
- Recommended current intensity: 3-5 mA
- Maximum current intensity may be determined by the size (surface area) of the active electrode
  - Current intensity may be set so that the current density under the active electrode falls between 0.1 - 0.5 mA/cm^2

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Current Intensity

- Increase intensity slowly until patient reports tingling or prickly sensation
- If pain or a burning sensation occurs, intensity is too great and should be decreased
- When terminating treatment, intensity should be slowly decreased to zero before electrodes are disconnected

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Treatment Time

- Treatment Time: ranges between 10-20 min.
- Patient should be comfortable with no reported or visible signs of pain or burning
- Check skin every 3-5 minutes for signs of skin irritation
- Decrease intensity during treatment to accommodate for decrease in skin impedance
  - This avoids pain or burning

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Dosage of Medication

- Dosage is expressed in milliampere-minutes (mA-min)
- Total drug dose delivered (mA-min) = *current* X *treatment time*
- Typical iontophoresis drug dose is **40 mA-min**

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Traditional Electrodes

- Older electrodes made of tin, copper, lead, aluminum, or platinum backed by rubber
- Completely covered by sponge, towel, or gauze which contacts skin
- Absorbent material is soaked with ionized solution (medication)
- If medicated ointment is used, it should be rubbed into the skin and covered by some absorbent material

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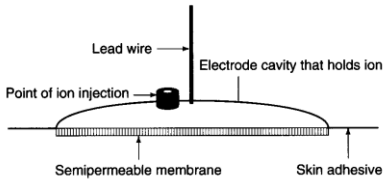
Commercial Electrodes

- Sold with most iontophoresis systems
- Electrodes have a small chamber covered by a semipermiable membrane into which ionized solution may be injected
- The electrode self adheres to the skin



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Skin Preparation

- Shave and clean skin prior to attaching the electrodes to ensure maximum contact
- Do not excessively abrade the skin during cleaning
- Damaged skin has lower resistance to current
  - Increased risk of burns

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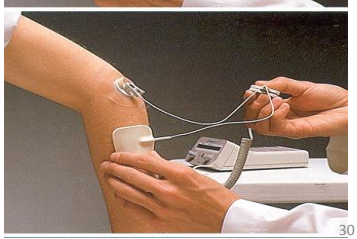
Electrode Preparation

- Attach self-adhering active electrode to skin



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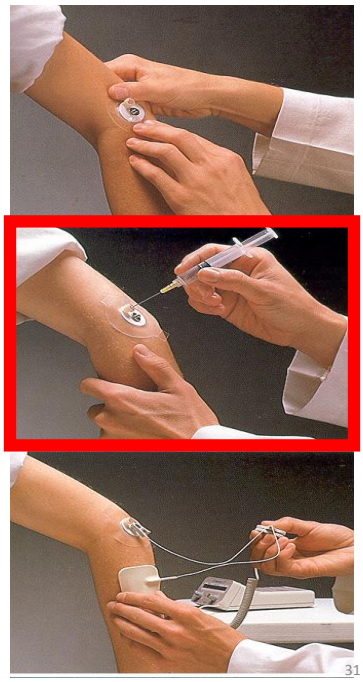
Electrode Preparation

- Attach self-adhering active electrode to skin
- Inject ionized solution into the chamber



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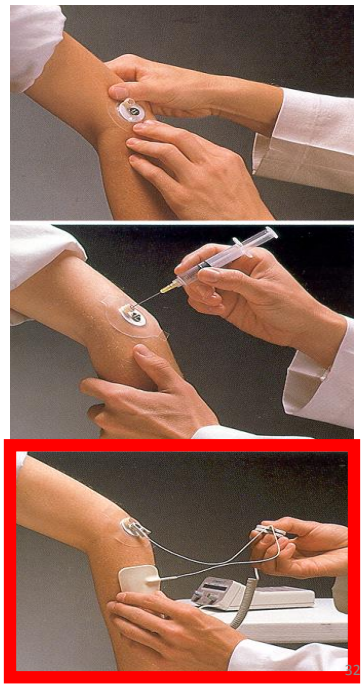
Electrode Preparation

- Attach self-adhering active electrode to skin
- Inject ionized solution into the chamber
- Attach self-adhering inactive electrode to the skin and attach lead wires from the generator
  - Must know polarity



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Electrode Placement

- Size of electrodes can cause variation in current density
  - Smaller = higher density
  - Larger = lower density
- Electrodes should be separated by at least the diameter of active electrode
  - ♦ Wider separation minimizes superficial current density
  - ♦ Decreased risk for burns

33

Selecting the Appropriate Ion

- Negative ions (medication) driven into tissues through the negative lead
  - Accumulation of negative ions in the tissues
- ♦ Produces an ***acidic reaction*** through the formation of hydrochloric acid
  - ♦ Results in hardening of the tissues by increasing protein density

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Selecting the Appropriate Ion

- Positive ions (medication) driven into tissues through the positive lead
  - Accumulation of positive ions in the tissues
- ♦ Produces an ***alkaline reaction*** through the formation of sodium hydroxide
  - ♦ Results in softening of the tissues by decreasing protein density
- ♦ Useful in treating scars or adhesions
- ♦ Some positive ions (medication) may also produce an analgesic effect

35

Selecting the Appropriate Ion

- Inflammation
  - ♦ Dexamethasone (-)
  - ♦ Hydrocortisone (-)
  - ♦ Salicylate (-)
- Spasm
  - ♦ Calcium (+)
  - ♦ Magnesium (+)
- Analgesia
  - ♦ Lidocaine (+)
  - ♦ Magnesium (+)
- Edema
  - ♦ Hyaluronidase(+)
  - ♦ Salicylate (-)
  - ♦ Mecholyl (+)
- Open Skin Lesions
  - ♦ Zinc (+)
- Scar Tissue
  - ♦ Chlorine (-)
  - ♦ Iodine (-)
  - ♦ Salicylate (-)

Prescription required

Table 9-1, p. 247

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Chemical Burns

- Most common problem = chemical burn
  - Occurs as a result of DC, not because of the ion being used
- ♦ Continuous DC creates migration of ions, which alters the normal pH of the skin
  - ♦ Chemical burns typically result from the accumulation of *sodium hydroxide* at the positive pole
- ♦ Minimize potential for chemical burn by increasing size of electrode
  - ♦ Decreases current density

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Thermal Burns

- Thermal burns may occur due to high resistance to current flow created by poor contact of the electrodes with the skin
- ♦ Minimize potential for thermal burns by…
  - ♦ Ensuring the electrodes are moist enough
  - ♦ Preventing wrinkles in the absorbent material impregnated with the ionic solution
  - ♦ Allowing adequate space between the active and inactive electrode
  - ♦ Preventing body weight on top of electrode

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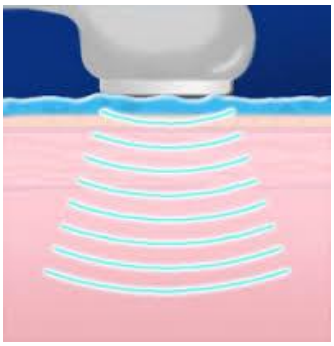
Sonophoresis (Phonophoresis)



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- Definition: sonophoresis is the enhancement of migration of drug molecules through the skin by ultrasonic energy
- Sonophoresis occurs because ultrasound waves stimulate micro-vibrations within the skin epidermis and increase the overall kinetic energy of molecules
- When sound is emitted at a particular frequency, the sound waves disrupt the lipid bilayers
- The higher the frequency, the more dispersed the transmission

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The skin

- Protective layer with large no. of dead cells, hence acts as barrier to penetration.
- The skin accounts for about 15% of adult's wt.
- Penetration varies with humidity, pigmentation, age, chemical status of all layers
- Stratum Corneum (SC) offers maximum resistance.
- SC consists of keratinocytes and lipid bilayer
- Permeability can be increased by Chemicals, Electrical Fields or Ultrasound which disrupt lipid bilayer of SC and increase permeability

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Advantages

1) Avoids variations associated with gastrointestinal absorption due to pH, enzymatic activity, drug-food interactions etc.
2) Substitute oral administration when the route is unsuitable as in case of vomiting, diarrhea.
3) Avoids hepatic "first pass" effect.
4) Avoids the risks and inconveniences of parenteral therapy.
5) Reduces daily dosing, thus, improving patient compliance.
6) Extends the activity of drugs having short plasma half-life through the reservoir of drug present in the therapeutic delivery system and its controlled release characteristics

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7) Rapid termination of drug effect by removal of drug application from the surface of the skin.

8) Can be used in emergencies. (e.g.. Non-responsive, unconscious, or comatose patient

9) Elimination of the hazards and difficulties of I.V. infusions or I.M. injections.

10) Enhance therapeutic efficacy, reduced side effects due to optimization of the blood concentration-time profile and elimination of pulse entry of drugs into the systemic circulation.

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11) Provide predictable activity over extended duration of time and ability to approximate zero-order kinetics.

12) Improved control of the concentrations of drug with small therapeutic indices.

13) Minimize inter and intrapatient variation.

14) Suitability for self-administration

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Limitations

Only limited number of potent drugs can be absorbed in therapeutic dose.
Many systemically effective therapeutic drugs produce skin irritation.
The drug must have some desirable physicochemical properties for penetration through stratum corneum.
If the drug dosage required for therapeutic value is more than 10mg/day, the transdermal delivery will be very difficult.
The barrier function of the skin changes from one site to another on the same person, from person to person and with age

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Sonophoresis: a historical perspective

- Sonophoresis was shown to enhance transdermal drug transport about 40 years ago by Fellinger and Schmidt who showed that application of ultrasound increases transport of hydrocortisone across the skin.
- 15 more drugs including steroidal anti-inflammatory drugs (hydrocortisone, dexamethasone), Non- steroidal anti-inflammatorydrugs (salicylates and ibuprofen),anaesthetic drugs (lidocaine),and protiens such as insulin were studied.
- Hofman and Moll who studied the percutaneous absorption of benzyl nicotinate.
- Bommannan et al. hypothesized that since the absorption coefficient of the skin varies directly with the ultrasound frequency

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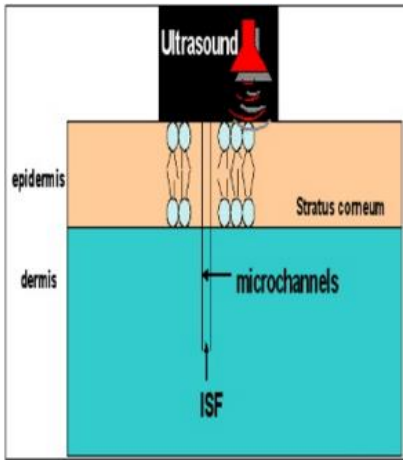
Understanding the drug delivery

- Sonophoresis or ultrasound can be used to create holes in the skin for fluids to travel into or out of the skin.
- By emitting sound at a particular frequency, the sound waves disrupt the lipid-bilayer of the stratus corneum (outermost layer of skin which has the most barrier properties), creating more and larger microchannels in the skin.
- Drugs can be administered through these channels



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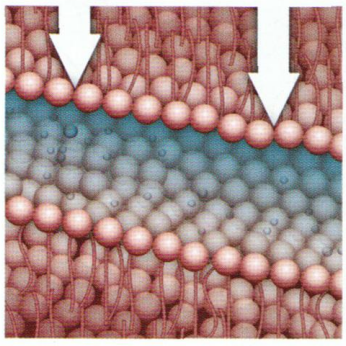
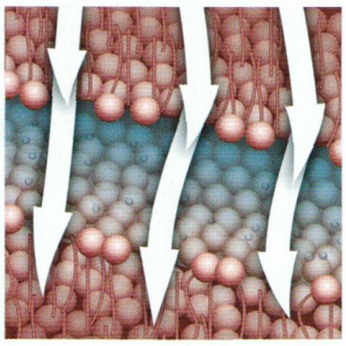


Lipid barrier impedes penetration



Openings in intracellular pathways enhance penetration

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Generation of ultrasound

- Ultrasound is a sound wave possessing frequencies above 20 kHz
- These waves are characterized by two main parameters, frequency and amplitude
- The waves used for sonophoresis which reduce the resistance offered by SC lie in the frequency range of 20 KHz to 20 MHz
- Ultrasound is generated with the help of a device called sonicator which is a AC electric signal generator.
- It produces a AC electric signal which is applied across a piezoelectric crystal i.e. transducer.
- The crystal undergoes rhythmic deformation due to electric current, producing ultrasonic vibrations.
- In the process of ultrasonic wave generation, electric energy is converted into mechanical energy in the form of oscillations, which generates acoustic waves.

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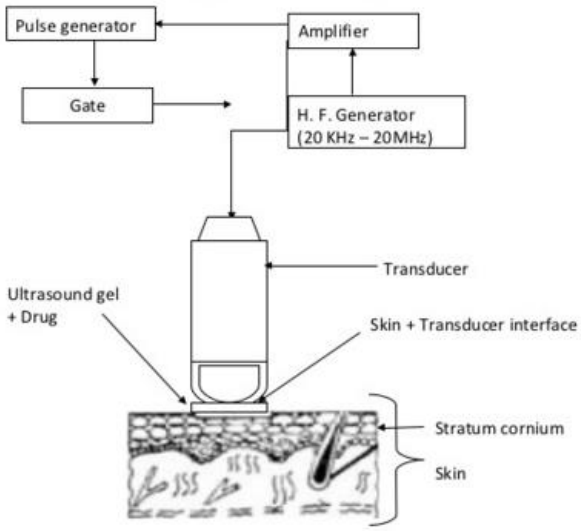
Ultrasonic generation system



50

- Ultrasound is applied by bringing the transducer in contact with the skin.
- For sonophoretic delivery, the desired drug is dissolved in a solvent and applied to the skin.
- The coupling medium can be the same as the solvent used to dissolve the drug or it can be a commercial ultrasound coupling e.g. gel.
- It helps to match impedence of tissue with the impedence of the transducer, so that the Ultrasound gets properly into the tissue.

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Selection of ultrasound parameters

(1) Ultrasound frequency
  - Therapeutic Frequency Ultrasound (1-3 MHz)
  - Low Frequency Ultrasound (Below 1MHz)
  - High Frequency Ultrasound (Above 3MHz)

(2) Ultrasound intensity :
  - Various ultrasound intensities in the range of 0.1 to 2 Watt/cm^2

(3) Pulse length
  - Ultrasound can be applied in a continuous or pulse mode. The pulse mode is frequently used because it reduces severity of side effects such as thermal effects.
  - It was also found that urea permeability of cuprophane membrane (a membrane made of regenerated cellulose, commonly used in hemodialyzers) increased from 6 to 56% as pulse length increased from 100 to 400 ms.

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Biological effect of ultrasound

- Significant attention has thus been given to investigating the effects of ultrasound on biological tissues.
- Ultrasound affects biological tissues via three main effects

(1) Thermal effect may important when,

(1) The tissue has a high protein content
(2) A high intensity of continuous wave ultrasound is used
(3) Bone is included in the heated volume
(4) Vascularization is poor

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(2) Cavitation effect may important when,

- Low-frequency ultrasound is used
- Grassy fluids are exposed
- Small gas filled space are exposed
- The tissue temperature is higher than normal

(3) Acoustic streaming may important when,

- The medium has an acoustic impedance different from its surrounding
- The fluids in the biological medium is free

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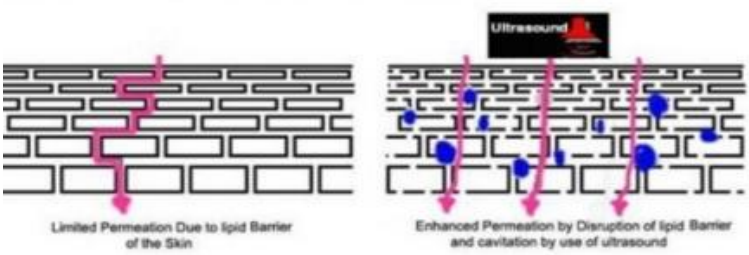
Mechanism of sonophoresis

(1) Cavitation

- Cavitation occurs due to the nucleation of small gaseous cavities during the negative pressure cycles of ultrasound
- This cavitation leads to the disordering of the lipid bilayers and formation of aqueous channels in the skin through which drugs can permeate



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- The minimum ultrasound intensity required for the onset of cavitation, referred to as cavitation threshold

a) Cavitation inside skin

- cavitation bubbles near the keratinocytes–lipid bilayers interfaces may, in turn cause oscillations in the lipid bilayers, thereby causing structural disorder of the SC lipids

b) Cavitation out side skin

- Cavitation bubbles can potentially play a role in the observed transdermal transport enhancement.
- These bubbles cause skin erosion, due to generation of shock waves, thereby enhancing transdermal transport

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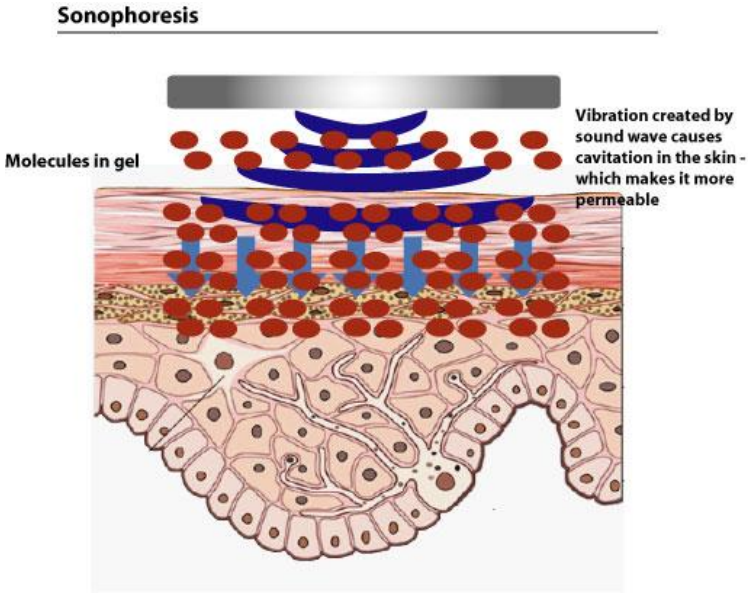

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- Cavitation is the formation of gaseous cavities in a medium upon ultrasound exposure.
- The primary cause of cavitation is the ultrasound induced pressure variation in the medium.
- Cavitation involves either rapid growth or collapse of a bubble or slow oscillatory motion of a bubble in the ultrasound field.
- Cavitation affects tissues in several ways.
- Specifically, collapse of cavitation bubbles releases a shock wave which can cause structural alterations in its surroundings

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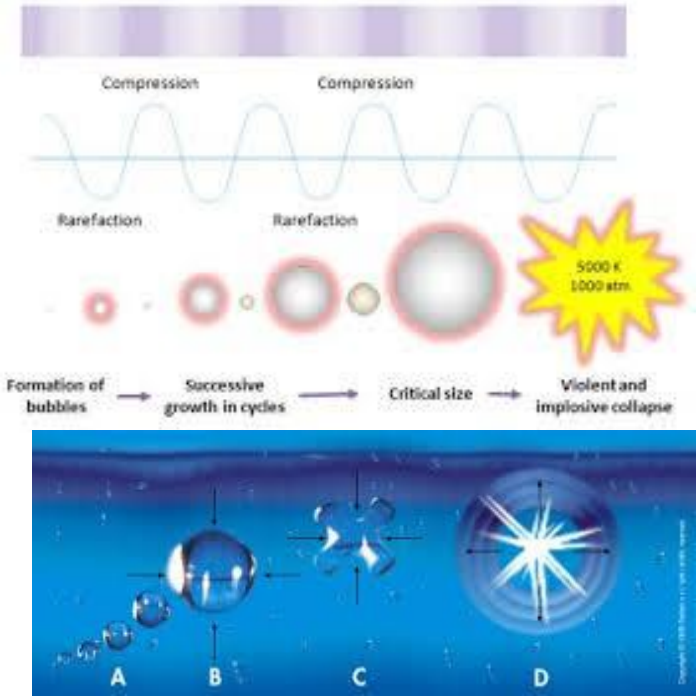

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Thermal effects

- Absorption of ultrasound results in a temperature increase of the medium.
- Materials with high ultrasound absorption coefficients such as bones, experience severe thermal effects compared to muscle tissues which have a low absorption coefficient.

60

- The absorption coefficient of a medium increases proportionally with the ultrasound indicating that the thermal effects of ultrasound are proportional to the ultrasound frequency.
- The increase in the temperature of a medium upon ultrasound exposure at a given frequency varies proportionally with the ultrasound intensity and exposure time.
- The thermal effects can be substantially reduced by pulsed application.

61

- Acoustic Streaming
  - Acoustic streaming, by definition, is the development of time-independent high fluid velocities in a medium under the influence of an ultrasound wave.
  - The primary causes of acoustic streaming are the reflections and other distortions of the wave propagation.
  - Oscillations of cavitation bubbles may also contribute to acoustic streaming. The shear stresses developed by streaming velocities may affect the neighboring structures

62

(2) Convective transport

- Fluid velocities are generated in porous medium exposed to ultrasound due to interference of the incident and reflected ultrasound waves in the diffusion cell and oscillations of the cavitation bubbles especially through hair follicles and sweat ducts
- Fluid velocities generated in this way may affect transdermal transport by inducing convective transport of the permeant across the skin, especially through hair follicles and sweat ducts.
- Experimental findings suggest that convective transport does not play an import ant role in the observed transdermal enhancement

63

(3) Mechanical stress

- Ultrasound is a longitudinal pressure wave inducing pressure variations in the skin, which, in turn, induce density variation
- Due to density variations, such as generation of cyclic stresses because of density changes that ultimately lead to fatigue of the medium
- Lipid bilayers, being self-assembled structures, can easily be disordered by these stresses, which result in an increase in the bilayers permeability

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Synergistic effect with other enhancer

(1) Chemical enhancer

- Enhanced Partitioning
- Lipid Bilayer Disordering
- Keratin Denaturation

e.g. Application of SLS alone for 90 min induced about 3- fold increase in mannitol permeability, while application of ultrasound alone for 90 min induced about 8-fold enhancement.

However, when combined, application of ultrasound from 1% SLS solution induced about 200-fold increase in skin permeability to mannitol

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(2) Iontophoresis

- Electrophoresis
- Lipid Bilayer Disordering
- Electroosmosis

e.g. The enhancement of heparin flux due to ultrasound + iontophoresis treatment was about 56-fold.

This enhancement was higher than the sum of those obtained during ultrasound alone (3-fold) and iontophoresis alone (15-fold).

Thus, the effect of ultrasound and iontophoresis on transdermal heparin transport was truly synergistic.

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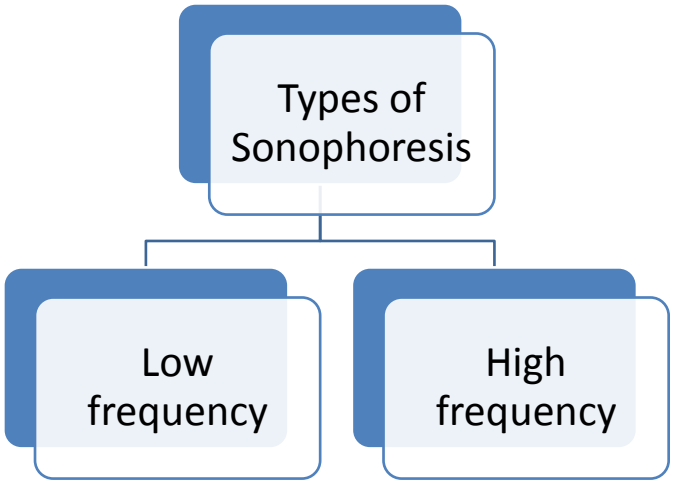

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Low frequency sonophoresis

1) Application of low frequency UltraS at 48kHz - Enhanced transdermal transport of lidocaine and insulin
2) Blood glucose level of a hairless rat immersed in beaker filled with insulin soln & placed in US bath (48kHz) decreased by 50% in 240 min.
3) Mitragotri has shown that application of even lower frequencies i.e.20 kHz enhances transdermal transport of low M.wt drugs like corticosterone, hydrocortisone& high M.wt protiens like insulin, interferon etc

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Enhancement of transdermal transport brought about by low frequency

- UltraS is more significant than therapeutic frequency UltraS.
- Comparison of enhancement ratios showed that enhancement brought by low frequency UltraS is upto 1000 fold higher than therapeutic frequency UltraS
- Cavitational effects in fluids are inversely proportional to UltraS frequency, hence play imp role in low frequency sonophoresis

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Exact Mechanism for higher efficacy of low frequency US

- Cavitation brought about by low frequency UltraS causes disordering of SC lipids.
- Oscillation of cavitation bubbles may cause significant water penetration into disordered lipid regions.
- This causes formation of aqueous channels through which permeants may pass- thus enhancing transdermal transport.
- That is the reason why low frequency UltraS can enhance transdermal transport of drugs which exhibit low passive permeability

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High frequency Sonophoresis

1)This region of ultrasound corresponds to a frequency higher than 3 MHz.

2)Absorption coefficient of UltraS varies directly with UltraS frequency, hence high frequency UltraS would concentrate more in epidermis leading to higher enhancements.

3)To asses this, effect of high frequency ultraS (2-15 Mhz) on permeability of salicylic acid through hairless guinea pig skin in vitro was studied and it was found that 20min application of UltraS at 2Mhz did not significantly enhance amount of salicylic acid penetrating the skin. But 10Mhz under same condition resulted in 4 fold increase

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Mechanism of High Frequency Sonophoresis

- Sonophoresis of lanthanum tracers across hairless mice at 16 Mhz was performed.
- Then the skin was observed under electron microscope after sonophoresis & it was found that Lanthanum tracer penetrated to dermal levels of skin & distributed within lipid bilayer.
- Hypothesis-Micronuclei(air pockets) present in the SC oscillate and collapse which results in enhanced skin permeation

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Therapeutic frequency of Sonophoresis

- Corresponds to frequency in the range of 1 to 3 MHz and intensity upto 2 W/cm^2.
- Sonophoresis of anti-inflammatory drugs was possible deeper into the tissue, especially muscles which are deep into the body.
- It was reported that application of UltraS in the therapeutic range delivered hydrocortisone about 5cm deep into pig tissues.
- This property has been used to deliver hydrocortisone to joints in treatment of rheumatoid arthritis

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Mechanism of therapeutic frequency sonophoresis

- Based upon cavitation experiments, it was concluded that cavitation inside the skin plays a major role in enhancing transdermal transport upon therapeutic sonophoresis.
- The exact mechanism was therapeutic frequency sonophoresis causes cavitation in the keratinocytes of the SC.
- Oscillation of the cavitation bubbles due to US causes oscillations in the lipid bilayer, causing structural disordering of the SC lipids.
- Shock waves generated by collapse of cavitation bubbles also contributes to structure disordering

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DEVICES USED IN SONOPHORESIS

- SonoPrep Skin Permeation Device:
- The SonoPrep device consists of a battery operated power and control unit, a hand piece containing the ultrasonic horn and the disposable coupling medium cartridge, and a return electrode.
- Ultrasonic hand piece attached to the patient's skin.
- The clinician pushes the hand piece down on the patient's skin to activate the ultra sonichorn

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- The patient holds the return electrode so that the device automatically shuts itself off, based on a drop in skin impedance once the proper level of skin permeation is achieved.
- Applies relatively low frequency ultrasonic energy to the skin for 15 seconds.
- Ultrsonic horn vibrates 55000 times per sec, applying energy to skin and creates cavitation bubbles that expand and contract which disrupts lipid bilayer creating reversible microchannels in skin through which fluids & analytes can be extracted & large drug molecules can be delivered.
- Easy for the health care professional to administer.
- The permeability is reversible, the skin goes back to its normal state within 24 hours.

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Safety

- The World Federation for Ultrasound in Medicine and Biology (WFUMB) has issued several publications related to safety of ultrasound bioeffects, addressing specifically thermal bioeffects and non-thermal bioeffects
  - Ultrasound affecting the structure of the skin: is it a reversible or irreversible change?
  - What is the role of the free radicals that are generated during the cavitation process within the skin?

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Applications

1) Sonophoresis is used in the treatment of damaged skin.
2) Hormone Delivery.
3) In surgery it helps in dissection, connection, built-up and treatment of biological tissue.
4) Low-Frequency Ultrasonic Gene Delivery.
5) Sonophoresis is also very useful in drug enhancement in granulomas and tumors. Most cancer therapy drugs act intracellularly.
6) Ultrasound is used for Calcific Tendinitis of the Shoulder.
7) The dolphin therapy and sonophoretic model.
8) Ultrasound Helps in Treating Tennis Elbow and Tendon Problem.
9) Helps in the treatment of damaged skin

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Table 1: Research on uses of sonophoresis to administer different drugs through the skin

Compound	Formul-ation	Experimental conditions	Membrane used	Results
Aldosterone (either ^{3}H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm^2, 100msec pulses applied every sec	Human cadaver skin *In vitro*	1400-fold increased in concentration of drug in skin
Arnica montana	Gel	1 MHz, 0.5 W/cm^2, P	Rat skeletal muscle	The massage with arnica gel proved to be an effective anti-inflammatory on acute muscle lesion in topic use, also show the ineffectiveness of Arnica Montana sonophoresis
Butanol (either ^{3}H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm^2, 100msec pulses applied every sec	Human cadaver skin *In vitro*	29-fold increased in concentration of drug in skin
Caffeine	Solution in pH 7.4 phosphate buffer	40 KHz, 0.44 W/cm^2, C	Hairless mouse skin *In vitro*	4-fold increased in concentration of drug in skin
Caffeine	Drug diluted in saline solution	20 KHz, 2.5 W/cm^2, P 20 KHz, 2.5 W/cm^2,	Human and hairless rat skin *In vitro*	Transdermal transport of drug was enhanced by both continuous and pulsed mode
Calcein & D_2O	Calcein dissolved in PBS	41-445 KHz, 60-240 mW/cm^2, 30 min	Excised hairless rat skin *In vitro*	The calcein flux was increased by 22.3-, 6.3-, and 3.8-fold at frequencies of 41, 158, and 445 KHz respectively
Corticosterone (either ^{3}H or ^{14}C labelled)	Solution of the radiolabelled permeant in PBS	20 KHz, 125mW/cm^2, 100msec pulses applied	Human cadaver skin *In vitro*	80-fold increased in concentration of drug in skin

Sr no	Sonophoresis	Iontophoresis
1	Sonophoresis is the enhancement of migration of drug molecules through the skin by ultrasonic energy	Iontophoresis is movement of ions of soluble salts across a membrane under an externally applied potential difference
2	Sonophoresis uses acoustic energy (ultrasound) to drive molecules into tissues	Iontophoresis uses electiral current to transport ions into tissues
3	Proper choice of ultrasound parameters including ultrasound energy dose, frequency, intensity, pulse length, and distance of transducer from the skin is critical for efficient sonophoresis.	Proper choice of electricity parameters including Current density, Current profile, Duration of treatment, Electrode material, Polarity of electrodes, is critical for efficient Iontophoresis
4	Sonophoresis usually employs a ultrasound between 20 KHz to 20 MHz	Iontophoresis usually employs a direct current between 0.5 mA to 5.0 mA
5	In sonophoresis drugs mixing with a coupling agent like gel, cream, ointment	In Iontophoresis drug is mix with solvent
6	The main mechanism for transport of drug is “Cavitation”	The main mechanism for transport of drug is “Electroporation”
7	Drug should be in aqueous or non aqueous and ionized or non ionized form	Drug must be in aqueous and must be in ionized form
8	Enhanced partitioning, Lipid bilayer disordering, Keratin denaturation etc. gives the synergetic effect of sonophoresis	Electrophoresis, Lipid bilayer disordering, Electroosmosis etc. gives the synergetic effect of Iontophoresis
9	Ultrasound can be applied in a continuous or pulse mode	Electrical current can be applied only in continuous mode
10	Sonophoresis mostly used for delivery of corticosteroids, local anesthetics and salicylates	Iontophoresis mostly used for hyperhydrosis diagnosis of cystic fibrosis, metallic and non-metallic ions

Intrauterine devices

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- Contraceptives are devices or methods for preventing pregnancy, either by preventing the fertilization of the female egg by the male sperm or by preventing implantation of the fertilized egg.
- Unintended pregnancy is expensive for both women and society in terms of medical costs, the costs of caring for more children, and achieving personal/professional goals

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- A wide variety of contraceptive methods has been developed, including:
  - Intrauterine devices (IUDs)
  - Intrauterine systems (IUS)
  - Hormonal contraceptives (oral contraceptives, implants, injections,
  - Contraceptive patch and vaginal rings)
  - Barrier devices with or without spermicides (male condom, diaphragm, cervical cap, female condom)
  - Natural family planning methods
  - Male sterilization (vasectomy)
  - Female sterilization (tubal ligation)

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- The intrauterine device (IUD) is one of the most effective, safe, and economical methods of contraception today.
- It is used by more women worldwide than any other reversible method of birth control.

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Historical background

- The modern era of the IUD started in 1909 when Richard Richter in Germany used a ring from silkworm gut as an intrauterine device.
- This device was the first genuine IUD.
- Unfortunately, Dr Richter's invention was of no medical interest at those times and had no impact on the practice of birth control, so clinical data were never supplied.

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- Ernst Gräfenberg described in 1929 a device consisting of a core of silkworm gut encircled by an alloy of copper, nickel, and zinc that was highly effective in preventing pregnancy.
- The results of his experiments started a strong controversy on the problem of the induction of PID (pelvic inflammatory disease) and European practitioners rejected the idea.

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- Fortunately, in Japan in 1934, Tenrey Ota presented the results of his studies on the use of elastic metallic rings as IUDs.
- The idea was accepted and the IUDs rapidly started to be used.
- After 1950, opinion about the IUD changed in Europe following the studies of Oppenheimer in Israel and Ishihama in Japan.
- These experiments and studies finally led to the first IUDs on the market in the 1960`s.

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Advantages

Highly effective.
Safe for most women.
Reversible and economical.
May be safely used by lactating and postpartum women.
Good choice for older women with COC precautions.
Long duration of use.
One visit for insertion and minimal follow up is required
Does not interact with medications.
Can be removed whenever the client chooses.

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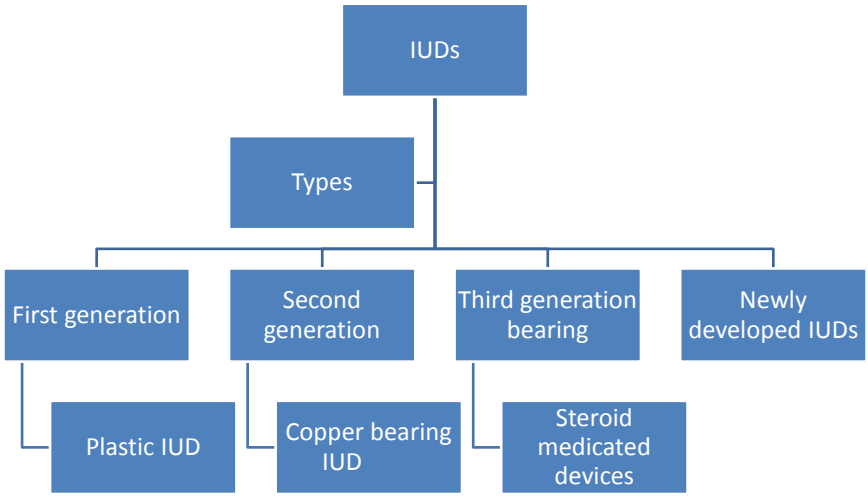
Limitations

Does not protect against STIs/HIV.
Pevlic Inflammatory Disease (PID) may occur if the woman has Chlamydia or gonorrhea at the time of IUD insertion.
May expose client to infection during insertion if infection prevention practices are not followed (this is minimal with good infection prevention procedures).
Trained provider dependent.
Some pain, cramping, minor bleeding on insertion.
Heavier/longer menstrual periods, increased cramping, and bleeding/spotting fairly common in some women during the first three months.
May contribute to anemia if a woman already has low iron blood stores before insertion and the IUD causes heavier monthly bleeding.
Rarely, the wall of the uterus may be punctured during IUD insertion. Unless severe, this usually heals without treatment.

91



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Mechanism of action

Non medicated IUDs	• Leads to foreign body reaction (produces sterile inflammatory response) which is spermicidal.
Copper IUDs	• Leads foreign body reaction & in addition produces alteration in cervical mucus & endometrial secretion, and initiates release of cytokine peptides known to be cytotoxic.
Hormone containing IUD	• Levonorgestrel IUD suppresses endometrium leading to atrophy & thickens cervical mucus hindering penetration

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Plastic devices: first-generation IUDs

- The first of the so-called “first generation” IUDs, represented by the “Margulies spiral”, was introduced in 1960.
- After many experiments, Dr Jack Lippes invented the double-S Loop (the Lippes Loop) in 1962
- It was made from polyethylene, with barium sulphate added for visibility under X-rays, and was available in four sizes, from A to D.
- This IUD was the first to have a nylon thread attached to the lowest part of the device; this made it easier to remove, and it was also possible to verify by simple vaginal examination that the IUD was in the uterine cavity.

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- Due to its particular shape (trapezoid), the Lippes Loop fits the relaxed uterine cavity snugly.
- The Lippes Loop was to become extremely popular and, of all the first-generation IUDs, had the greatest worldwide impact.

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- In subsequent years, resourceful investigators produced scores of original, and sometimes peculiarly shaped, plastic IUDs.
- One of these was the Dalkon Shield, developed by Dr Hugh Davis, and released in 1971.
- The Dalkon Shield was a plastic device which looked like a round bug with one large eye and five legs on each side.
- It had a unique tail: not a single filament, but many fibres wound together and enclosed in a sheath.

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- Because the Dalkon Shield's unique shape made it difficult to remove, a multifilament string was used (instead of the usual stiff monofilament polyethylene thread) to provide increased tensile strength during removal.
- The multifilament tail string, unique to the Dalkon Shield, was most probably responsible for the facilitated ascent of bacteria from the vagina upward into the uterine cavity, causing pelvic infections.
- Shortly after its release, infections reached a serious level

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Copper-bearing devices: Second generation IUDs

- Towards the end of the 1960's, it was discovered that adding copper to the plastic produced an IUD that was more effective in preventing pregnancy and less frequently caused bleeding problems.
- The development of the first copper-bearing IUD (Cu-IUD) was announced in 1969 by Dr Jaime Zipper and Dr Howard Tatum.
- Dr Tatum invented the plastic T–IUD and Dr Zipper investigated the device clinically

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- Being aware that the uterine cavity, when contracted, assumes the shape of a capital “T”, Dr Tatum postulated that a small T-shaped IUD would be the most appropriate.
- Moreover, and on account of the “fundal-seeking effect”, the T-shaped device would be less prone to expulsion.
- After some dose-exploration experiments, the team decided that a copper filament with a free (ionizable) surface of 200 mm^2 was optimal in terms of contraceptive efficacy.
- The first copper-bearing IUD, the TCu200, was produced in 1969.

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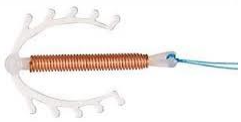

- Later, an impressive number of “copper-bearing IUDs” were devised, of which only a few have made a clinical career.
- The Multiload (ML) IUD invented in 1974 by the Dutch gynaecologist Dr Willem van Os, was very successful.
- Its platform is an ingenious hybrid of the T-IUD and the Dalkon Shield, the purpose of the ear-of-corn-shaped skeleton being two-fold: to avert traumatic pressure on the endometrium while enhancing the retention of the device.

100

- The Multiload (ML) series of devices were designed to reduce the incidence of expulsion by the addition of plastic fins on the lateral, curved arms.
- Copper wire is wound onto the central stem of the device. The
- MLCu-250 was the first version, available in three sizes (standard, mini and short), to allow insertion into different sized uteri, including the nulliparous. Can be used for – 3 years
- The MLCu-375 followed, with more copper to enhance efficacy and length of use. Can be used for 5 years

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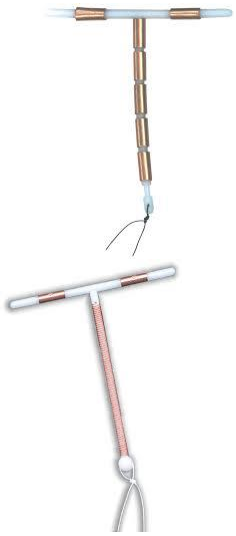
- Over the years, Dr Tatum himself developed a series of copper bearing T devices.
- His TCu220C model is of particular interest, because, in carrying copper collars instead of a copper filament, metal loss was prevented.
- In his more flexible model, Dr Tatum combined tubular with filamentous copper and the TCu-380A currently serves as the gold standard for comparative studies.



102

- The Copper T 380 series comprises three devices :
  - TCu-380A, the original device
  - A device with a silver core wire (in two variants: TCu-200-Ag and TCu-380Ag),
  - TCu380S (Slimline).
- The current license for the TCu380A is for up to eight years.
- The TCu-200-Ag has been in use since 1978.
- It consists of a plastic T-shaped frame with silver-cored copper wire wound around its central stem, presenting a total surface area of 200 mm^2 copper.
- The addition of the silver core was found to reduce fragmentation, thus prolonging the effective lifespan of the device

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- In the early 1990s, a higher load, but otherwise identical, device, the TCu-380-Ag, was developed, bearing a surface area of 380 mm^2 copper.
- The TCu-380Ag is made of polyethylene and wound with copper wire with a silver core.
- The surface area of the copper is 380 mm^2.
- The polyethylene body, shaped as a modified T, is impregnated with barium sulphate.
- Removal threads, pigmented with iron oxide, are attached to the base of the vertical arm of the T.
- The current license for the TCu-380-Ag is for up to five years.

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- The Slimline (TCu380S) was so called because the copper collars on the side arms were sunk into, and thus flush with, the side arms, making loading into the insertion tube easier

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Steroid-medicated devices: third generation IUDs

- In the late 1960s, Dr Antonio Scommegna, having demonstrated the uterine effects of progesterone, postulated that the endometrial atrophy elicited by the natural steroid hormone would be useful in preventing implantation and reducing menstrual bleeding.
- He developed a hormone releasing device and showed that it is as effective in preventing pregnancy as the copper-bearing IUD.

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- Dr Scommegna devised a T-shaped device, consisting of a permeable polymer membrane which releases progesterone at a predictable, controlled rate of 65 mg per 24 h over the period of a year.
- Unfortunately, this IUD did not gain wide popularity on account of its short (1-year) effective lifespan

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- The levonorgestrel IUS is a T-shaped polyethylene device with a steroid reservoir around the vertical stem.
- The cylindrical reservoir contains a mixture of silicone (polydimethylsiloxane) and 52 mg levonorgestrel, a progestin widely used in implants, oral contraceptives, and vaginal rings.
- This allows a steady, local release of 20 μg levonorgestrel per day through the rate-limiting surface membrane.
- The reservoir is covered by a silicone membrane, and the frame contains barium sulphate, which makes it radiopaque.
- A monofilament removal thread is attached to a loop at the end of the vertical stem.
- The LNG IUS is licensed for 5 years' use.

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Newly developed IUDs

- Several new intrauterine devices (IUDs) are under development or in the early marketing phase.
- These new devices contain various modifications designed to improve patient continuation and physician satisfaction.
- Modifications include those designed to facilitate easier insertion and removal, to decrease the rates of accidental expulsion, and reduce complaints of pain or bleeding (responsible for 30 % to 50 % of discontinuations).
- Devices are being designed to address these issues by modifying IUD size, shape, and flexibility.

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CuSafe 300

- This device was developed specifically to decrease the incidence of unwanted side effects such as bleeding, pain and expulsion.
- The plastic frame of the device is smaller and more flexible than most other framed devices.
- Both ends of the device's transverse arms curve inwards to reduce uterine tissue irritation.
- The side arms are thinner than the central stem, allowing easier insertion by a simple push-in technique, and are bent back on themselves in order to reduce trauma to the endometrium.
- This design facilitates easier and less painful insertion and removal, but the curved, "fundal-seeking" arms also resist expulsion.
- The device bears 300 mm^2 copper on its central stem.
- It carries a recommended lifespan of 5 years.

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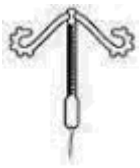
Fincoid-350



- The Fincoid-350, is also designed to resist accidental expulsion.
- The IUD has a plastic skeleton comprised of two parts:
  - Curved horizontal arms
  - A copper-coated vertical stem.
- The horizontal arms lock into a groove on the vertical stem.
- The resulting movable joint easily constricts and expands with uterine contractions, adjusting to variations in uterine size and shape.
- The Fincoid-350 comes in two sizes: standard and short

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GyneFix®

- To minimize failure and side effects of intrauterine devices (IUDs), especially abnormal bleeding, pain, partial and complete expulsion, and other complications due to disharmony, the “frameless” intrauterine system (IUS) was developed
- Total elimination of the frame would create perfect harmony and reduce the surface area of the foreign body.
- However, to retain the IUS in the uterine cavity, the device should be fixed to the uterine wall.
- This approach seemed a logical and practical way to obtain a significant improvement in IUD performance.

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- This “frameless” IUD consists of six 5 mm copper sleeves with an effective copper surface area of 330 mm^2, fixed on a length of semi-rigid suture thread.
- The proximal end of the suture contains a knot that is inserted 1 cm into the fundal myometrium to anchor the device into the uterine muscle.
- Due to its frameless design, flexibility, and minimal presence in the uterine cavity, this IUD is associated with few expulsions

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