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DEVICE FOR TRANSDERMAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT
Now-a-days, the skin is consider as a major route for administration of many drugs. Transdermal drug delivery has many potential advantages, but the skin's poorly-permeable stratum corneum blocks delivery of most drugs at therapeutic levels. To overcome these problems regarding transdermal drug delivery system, various approaches has been developed. These approaches mainly includes, use of chemical penetration enhancers, mechanical stimulations, and many more. This review article mainly focuses on various devices which are used to increase the permeation of the drug through the skin. This devices includes microscale devices, electrical devices, iontophoresis, ultrasound, laser radiation, radio frequency, etc.

KEYWORDS: Dermal, skin, permeability, various techniques.

INTRODUCTION[2,5]
Transdermal drug delivery systems encompass a wide array of non-invasive or minimally invasive technologies for delivering drugs and vaccines across the skin without needles. But Skin has evolved to be a highly effective barrier around the human body.

1] The skin barrier[5]
The barrier function of the skin is reflected by its multilayered structure. The top or uppermost layer of the skin known as the stratum corneum (SC). It is composed of dead cells within lipid rich matrix. Lipophilic nature of the SC, which primarily accounts for the barrier properties of the skin.

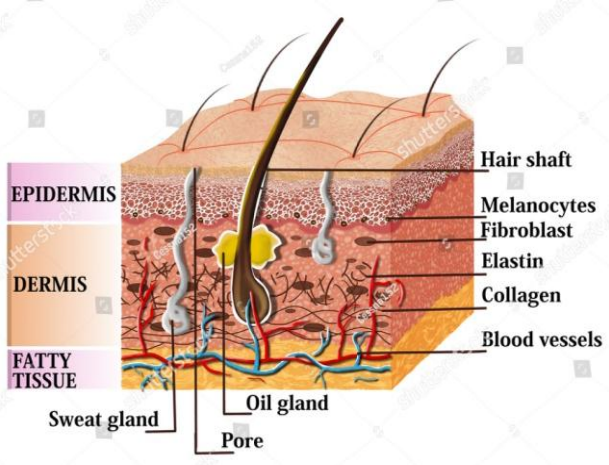


Fig. Anatomy and physiology of human ski.

2] Various Types of Devices
I) Iontophoresis[1,5,6,11,12]
Principle
It is electrical driving of charged molecules into tissue, passes small amount of current (approximately 0.5 mA / cm^2) through a drug containing electrode in contact with a skin. Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: electrorepulsion (for charged solutes), electroosmosis (for uncharged solutes) and electropertubation (for both charged and uncharged). Iontophoresis, is ideally suited to facilitate the transport of hydrophilic ionisable molecules that are usually not good candidates for passive transdermal delivery.

Components
i) Two electrodes, anode (positively charged) and cathode (negatively charged)
ii) Microprocessor, battery or power supply
iii) Drug reservoir.

Working
These electrodes are named as 'active' and 'return'. 'Active' electrode contains drug formulation and 'return' electrode is placed on the skin and thus, the circuit is completed. Applied electric field causes flow of electric current generated by ions present in formulation and in the skin. This is referred to as electromigration. Unlike other enhancement methods, this acts on the molecules by applying second driving force that is electrical potential gradient along with concentration gradient across the skin.

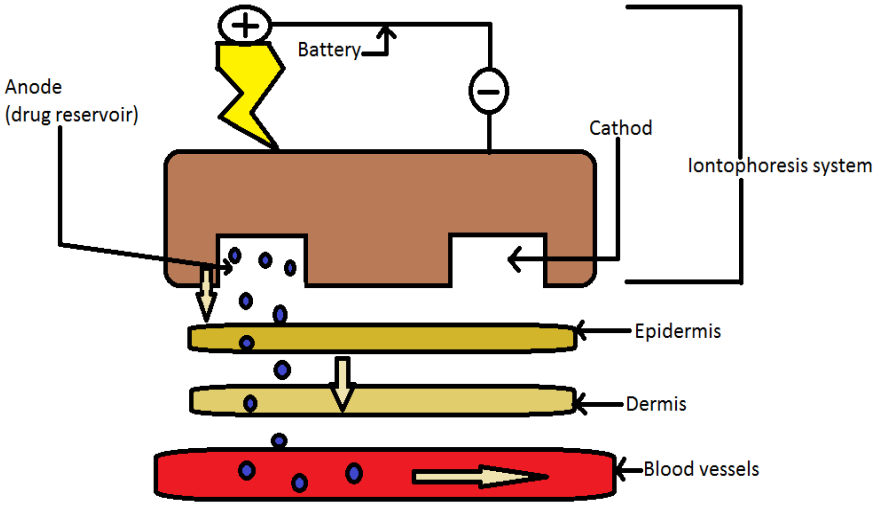


Fig. iontophoresis system.

Merits

i) Possible delivery of therapeutic peptides
ii) Delivery of polar neutral molecules
iii) Delivery of local anaesthesia
iv) Portable and efficient system
v) Increased patient compliance

Demerits

i) Can damage hair follicles
ii) Problem of home use
iii) Regulatory limits of amount of current
iv) Failed to improve permeation of macromolecules
v) Irreversible damage to the barrier properties of the skin

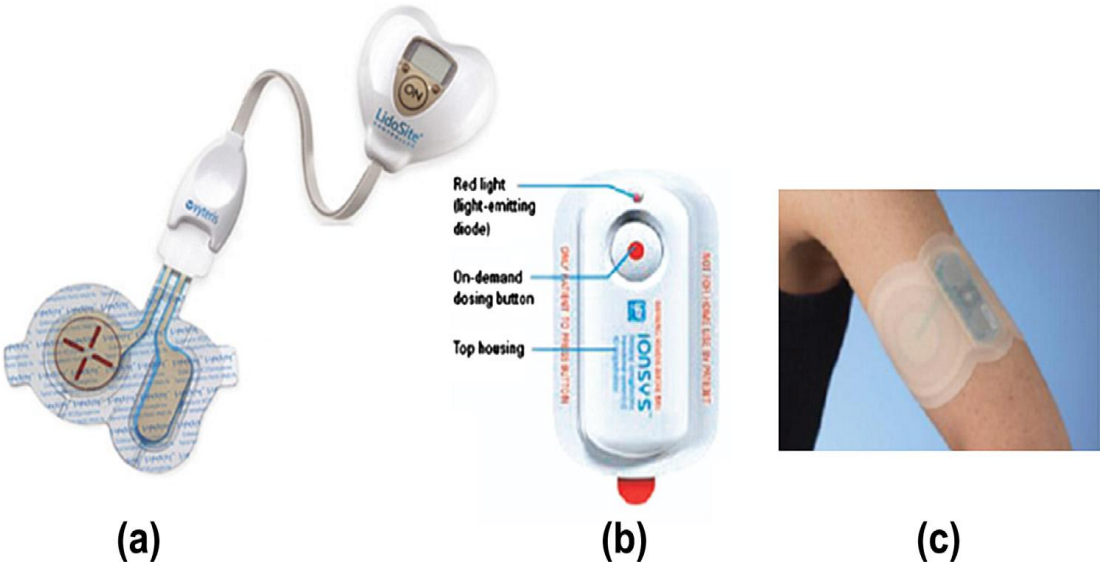
Applications

i) Possible transdermal delivery of therapeutic peptides, proteins and oligonucleotides.
ii) Delivery of polar neutral molecules
iii) Delivery of local anaesthesia like lidocaine-epinephrine

(a) The first prefilled commercial iontophoretic patch systems approved by the FDA was LidoSite™ (V yteris Inc., FairLawn, NJ, USA), which provided rapid local delivery of lidocaine for fast dermal anaesthesia. The system consisted of a disposable pre-filled patch, re-usable battery-powered controller and a flexible interconnect module.

(b) The second pre-filled iontophoretic system that was approved by the FDA was Ionsys™ (Alza, Mountain View, CA, USA). This was a fully-integrated single-use iontophoretic system for the systemic delivery of fentanyl to enable patient controlled analgesia for the fast relief of post-operative pain and provided a non-invasive alternative to the use of morphine pumps.

(c) A third iontophoretic system, Zecuity™ (Nu Pathe Inc., Cons-hohocken, PA)has developed for the electrically assisted delivery of sumatriptan, an anti-migraine drug.



II) Ultrasound[1,5,13,14]

Principle

This involves use of ultrasonic energy which facilitates transdermal delivery of drug molecules and it is referred as sonophoresis or phonophoresis. The mechanism of increase in skin permeability is formation of gases cavities within intercellular lipids on exposure to ultrasound results in disruption of SC. Frequencies between 20 kHz – 16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (<100 kHz) are believed to have a more significant effect on transdermal drug delivery, with the delivery of macromolecules of molecular weight up to 48 kDa being reported.

Components

Consists of –

i) Control unit
ii) Ultrasonic horn
iii) Control panel
iv) Disposable coupling cartridge
v) Return electrode

Working

Ultrasonic horn is applied to the patient's skin. Gel is applied prior to facilitate easy application of ultrasound probe. This creates ultrasonic waves which creates pores in the skin. Drug can be given in patch like system or semisolids spreaded on the skin. Because of pores creation in the skin, drug will permeate fastly.

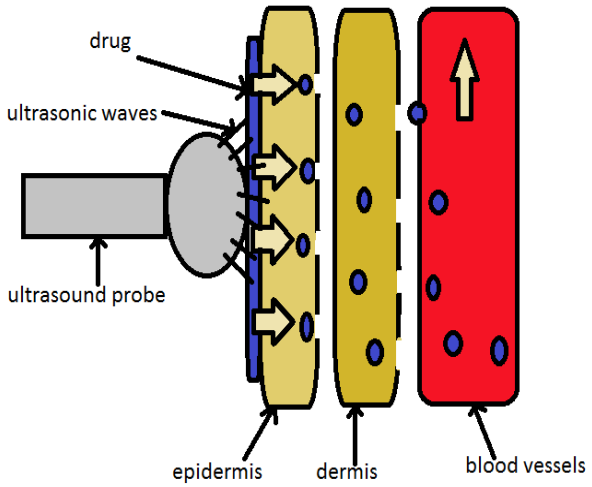


Fig: Ultrasound system.

Merits

i) Delivery of high molecular weight drugs
ii) Used for hydrophilic drugs
iii) For large polar drugs

Demerits

i) Validation of system needed
ii) Not for home use

Applications

i) Transdermal delivery of proteins
ii) Transdermal delivery of insulin
iii) Deactivation of some skin enzymes
iv) Local anaesthetic

III) Electroporation[1,5,10,15,16]

Principle

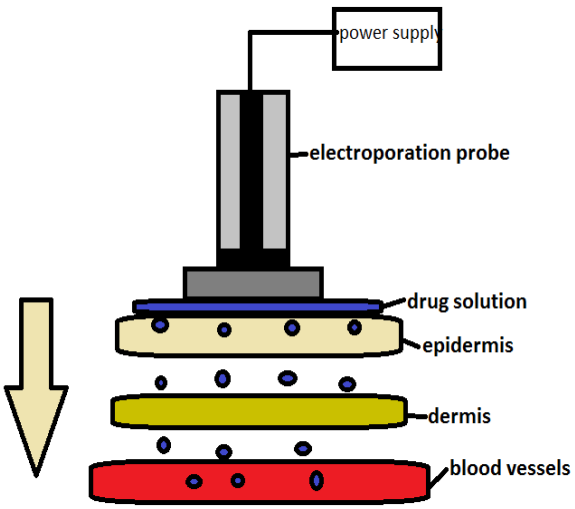
It involves creation of transient aqueous pathways in lipid bilayer membrane by application of small amount of current impulses. These electrical pulses are approximately 100-1000 V/cm. These formed pores provides pathway for drug penetration. Electroporation occurs when transmembrane voltage reaches a few hundred millivolts for electric field pulses typically of 10 µs or 100 ms duration.

Components

i) Power supply
ii) Electrodes
iii) Probe

Working

Drug solution is spreaded on skin and probe of electroporation is placed on skin. Due to electric pulses, electric field is generated which forces drug to permeate through the skin.



Figure, electroporation technique.

Merits

i) Penetration of peptides
ii) Fluxes increases for neutral highly charged molecules

Demerits

i) Home use is problematic
ii) Possible skin damage
iii) Safety and efficacy of method

Application

i) Delivery of vaccines, liposomes, micromolecules, nanoparticles.
ii) Delivery of Physostigmine

iii) Delivery of peptides like vasopressin, neurotensin, calcitonin,etc.
iv) Gene delivery
v) pplication of cosmetics.

IV) Magnetophoresis[1,5,17]
Principle
This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin.[5] Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability.

Components
i) Magnet

Working
Drug solution is spreaded on the skin surface and magnetic field is generated by keeping two magnets on either side. Due to generation of magnetic field, drug flux is increases through the skin.

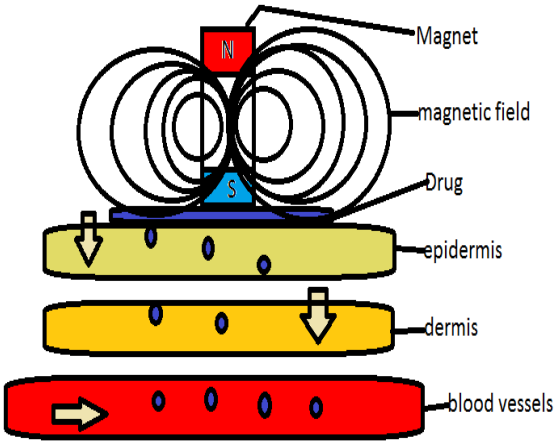


Fig. Magnetophoresis System.

Merits
i) Can deliver drug in controlled and pulsatile form.
ii) Easy for the application.

Demerits
i) This technique can only be used with diamagnetic materials.

Application
i) Enhancement in benzoic acid flux.
ii) Increased permeation of Terbutaline Sulphate.

V) Photomechanical Waves[1,5,18]
Principle
Lasers have been used in clinical therapies for decades, and therefore their effects on biological membranes are well documented. Lasers are frequently used for the treatment of dermatological conditions such as acne and to confer "facial rejuvenation" where the laser radiation destroys the target cells over a short frame of time.

Components
i) Portable laser
ii) Laser radiation generator

Working
Drug solution is spreaded on the skin surface. Photomechanical waves from the laser source are emitted. Due to these waves, drug solution get absorbed through the skin.

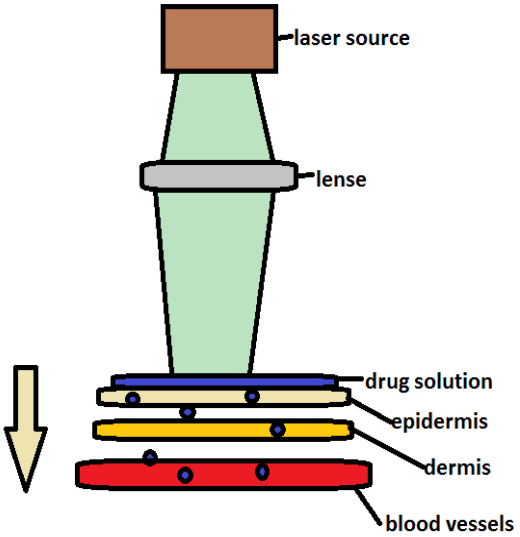


Figure: Photomechanical technique.

Merits
i) No damage to underlying epidermis.
ii) Hand-held portable device

Demerits
i) Technique is likely to remain experimental.
ii) Sometimes, damage to the skin.

Applications
i) For facial rejuvenation.
ii) Topical application of anaesthesia
iii) Delivery of Insulin.

VI) LIQUID JET INJECTORS[2,19]
Principle
Liquid jet injections employ a high-speed jet to puncture the skin and deliver drugs without the use of a needle. two main classes of liquid jet injectors have been developed. These are single-dose jet injectors, known as DCJIs (disposable cartridge jet injectors) and MUNJIs (multi-use-nozzle jet injectors).

Components
i) Power source
ii) Piston
iii) Drug loaded compartment
iv) Nozzle

Working

Upon triggering the actuation mechanism, the power source pushes the piston which impacts the drug-loaded compartment, thereby leading to a quick increase in pressure. This forces the drug solution through the nozzle orifice as a liquid jet with velocity ranging between 100 and 200m/s. Upon impinging on skin, the jet punctures through the skin and initiates hole formation. The formation of a hole is believed to be due to a combination of skin erosion and fracture and is completed during the first few hundred microseconds. As the jet progresses deeper in the skin, velocity decreases until it does not have sufficient energy to continue hole formation. Thus, drug is permeate through the skin.

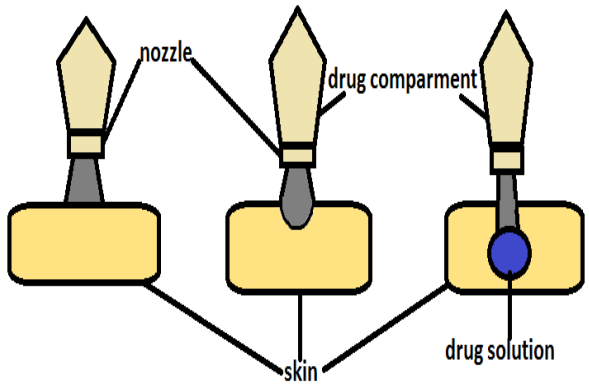


Figure: Liquid jet injector technique.

Merits

i) Faster delivery of drug.
ii) Minimum pain

Demerits

i) Reaction at the site of application.
ii) Sometimes pain and bruising of the skin.
iii) Bleeding and haematomas.

Applications

i) In case of measles, smallpox, cholera, hepatitis B, influenza and polio. DCJIs have been used for delivery of several proteins.
ii) Delivery of insulin and growth hormones, erythropoietin and interferon.

VII) Powder Injectors[2,20]

Principle

Powder jet injectors deliver vaccines or drugs in dry powdered form into superficial layers of skin. The terms biolistic injectors and gene guns have also been commonly used for these injectors, with the latter term used exclusively for DNA delivery.

Components

i) Compressed gas as the power source.
ii) A drug compartment containing particulate drug formulation,
iii) A nozzle to direct the flow of particles.

Working

The drug compartment is closed with diaphragms on either side, which are typically few microns thick. Upon triggering the actuation mechanism, compressed gas from a storage canister expands and pushes against the diaphragms, sequentially rupturing them. The flowof gas carries the drug particles with it. The particles then exit through a nozzle and impinge on skin .Upon impacting on the skin, particles puncture micronsized holes into stratum corneum by virtue of their momentum. Some particles are contained in stratum corneum while a significant percent reach the viable epidermis for the desired therapeutic effect.

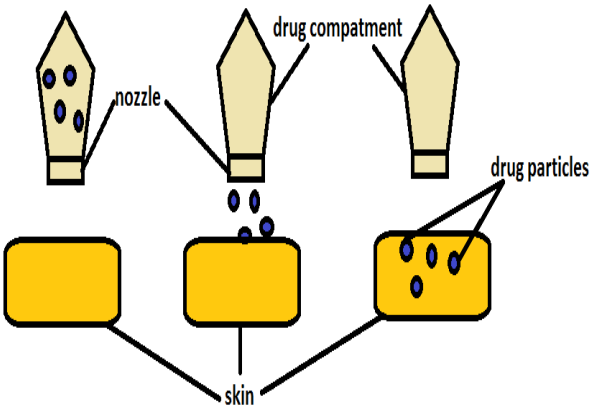


Figure: Powder jet injector technique.

Merits

i) Painless delivery
ii) Powdered drug can be given transdermally.

Demerits

i) Post injection symptoms.
ii) Mild erythema, hyper-pigmentation, flaking and discoloration at the injection site.
iii) mild tingling, tightening or burning.

Applications

i) DNA vaccines delivery
ii) Induction of humoral and cell mediated immune response against influenza, hepatitis B and rabies.
iii) protein delivery, gene therapy.

VIII) Microneedles[2,5,6,8]

Principle

Micron-scale needles that are employed for transdermal vaccination and drug delivery. These microneedles of length 50–110 mm will penetrate the SC and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel or solid particulates. Microneedles differ in design and composition and can be classified in four major categories: solid microneedles used to pretreat the skin , drug-coated microneedles, dissolving or biodegradable microneedles and hollow microneedles.

Components
i) Microneedles
ii) Drug reservoir

Working
Solid microneedles can either be pressed onto the skin or scraped on the skin for creating microscopic holes, thereby increasing skin permeability. The second strategy is to have vaccines or drugs encapsulated. This coating can dissolve within 1min after insertion into skin, after which the microneedles can be withdrawn and discarded.

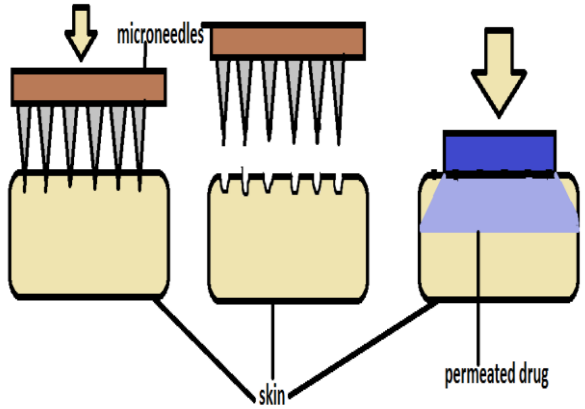


Figure. Microneedles technique.

Merits
i) Most designs of microneedles are painless.
ii) Can give controlled drug release.
iii) Effectively enhance the delivery of many therapeutic molecules across biological membranes.

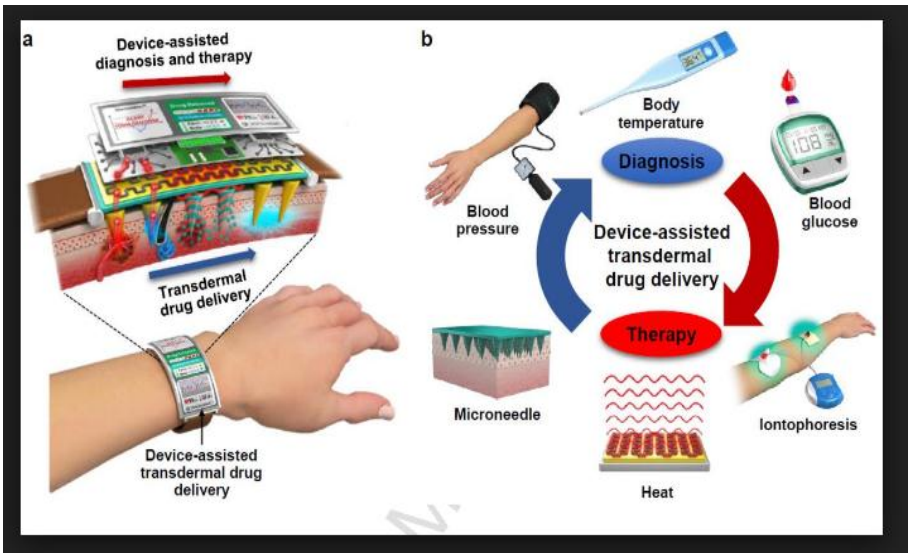
Demerits
i) Fabrication of microneedles is delicate task.
ii) Question of cost.
iii) Sometimes, become painful.

Applications
i) Delivery of naltrexone.
ii) Delivery of low molecular weight drugs, proteins, DNA, virus particles and micro-particles.
iii) Delivery of erythropoietin and enzymes.
iv) Insulin delivery.
v) Lidocaine delivery to induce local anesthesia.

IX) Wearable Devices[4,21,22]
Principle
Health-monitoring devices in the form of wearable pads, wrist-bands and straps that provide long term continuous recordings of electrophysiological activity and acute physiological responses have significantly improved our understanding of diseases, including heart failure, epilepsy and Parkinson's disease. Various types of sensors have been incorporated in wearable devices. Also some drug release actuators are also available.

Components
It may contain one or more of the following components –
i) Heart beat sensor
ii) Glucose level sensor
iii) Strain sensor
iv) Temperature sensor
v) Electroresistive heaters

Working
According to the sensor present in the device, it will act likewise. This device will measure heart beats, body temperature, glucose level and will release drug formulation according to it.



Merits
i) Increased patient compliance.
ii) Absolutely painless.
iii) Drug release according to the monitored levels.

Demerits
i) Question of cost.
ii) Sometimes, recording of data does not work properly.

Applications

i) Recording of heart beats
ii) Recording of glucose level via sweat.
iii) To increase permeation of various drugs.

The following table will give idea about the molecular weight and examples of the drug that can be deliver by that specific technique.

Sr no	Name of the technique	Molecular weight (Da)	pKa	Examples of drug
1	Iontophoresis	149 to 3600	-1.37 to 8.5	Lidocaine, Botulinum, Epinephrine, NSAIDs
2	Ultrasound	74 to 5800	2.97 to 16	Aldosterone, Butanol, Corticosterone, Estradiol, Insulin
3	Electroporation	102 to 5800	-3.1 to 9.6	Timolol, Doxepin, Fentanyl, Cisplatin, Insulin
4	Magnetophoresis	234 to 323	1.9 to 8.1	Lidocaine, Terbutaline sulphate
5	Photomechanical wave	848 to 48000	-3.6 to 11.7	Insulin, Erythropoietin, Dextran
6	Liquid jet injector	800 to 5800	-3.6 to 11.7	Insulin, Erythropoietin, Dextran
7	Powder jet injector	800 to 5800	-3.6 to 11.7	Insulin, Erythropoietin, Dextran
8	Microneedles	234 to 5800	-1.37 to 11.6	Lidocaine, Naltrexon, Insulin, Erythropoietin.

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