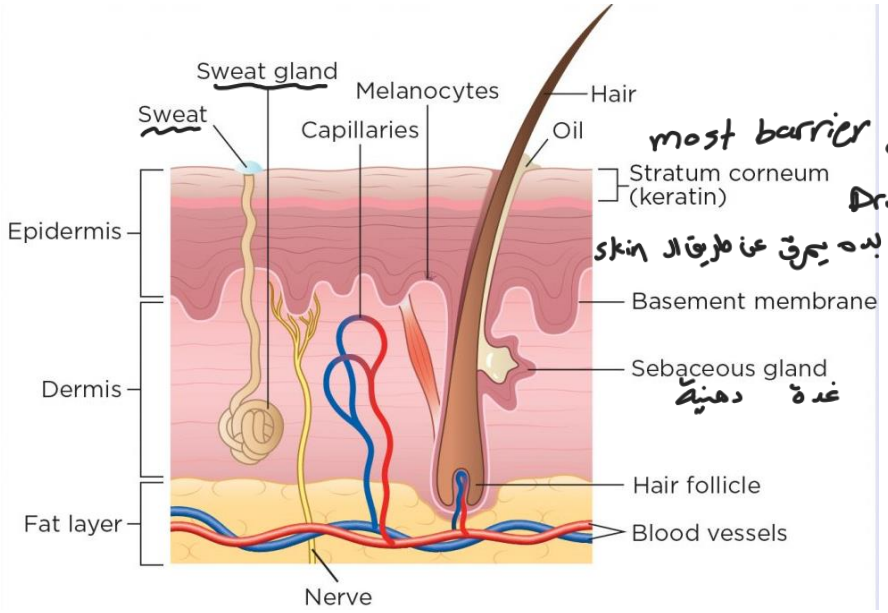
Transdermal Drug Delivery Systems

Introduction

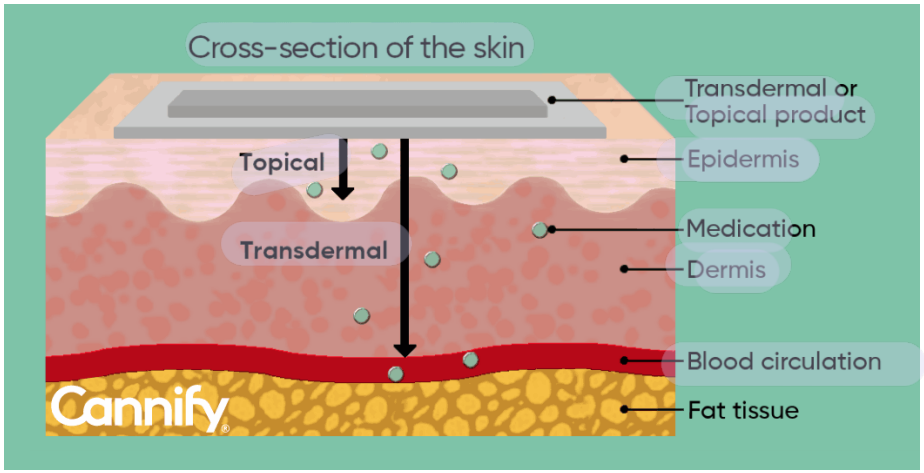
- Structure of the skin:
- Skin is the most accessible and largest organ of the body with a surface area of 1.7 m^2, compromising 16% of the total body mass of an average person.
- The main function of the skin is to provide a protective barrier between the body and the external environment
- Skin layers:

1. Epidermis
2. Dermis
3. Hypodermis.



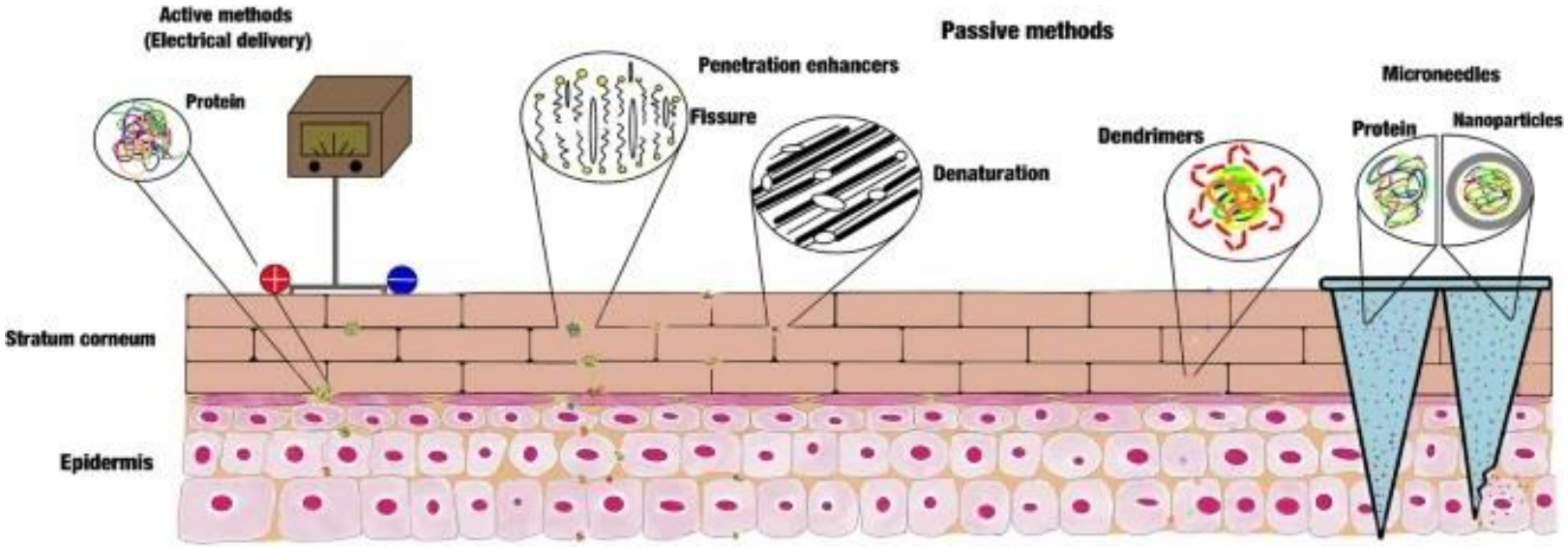
Introduction

- Transdermal drug delivery (TDD) is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin.
- The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis.
- When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation



Introduction

- Transdermal drug delivery system (TDDS) are systems that utilize skin as a site for continuous drug administration into the systemic circulation.



Current application of TDD

The TDD market has had a considerable impact on the delivery of numerous drugs, primarily in the fields of:

- Pain management
- Hormonal applications
- Central nervous system disorders (Parkinson's disease→ rotigotine, Alzheimer's disease →Rivastigmine)
- Cardiovascular diseases (Anti-angina → Nitroglycerine, Hypertension→ Clonidine)
- Smoking cessation (Nicotine)
- Motion Sickness (Scopolamine)

مضاد للذبحة الصدرية

الدواء لعلاج الـ Motion sickness

application أول على موضوع TDDs

Transdermal drug transport pathways

There are two possible routes of drug penetration across the intact skin:

A. Trans-epidermal pathways

1. Intracellular route:

   allows the transport of hydrophilic or polar solutes

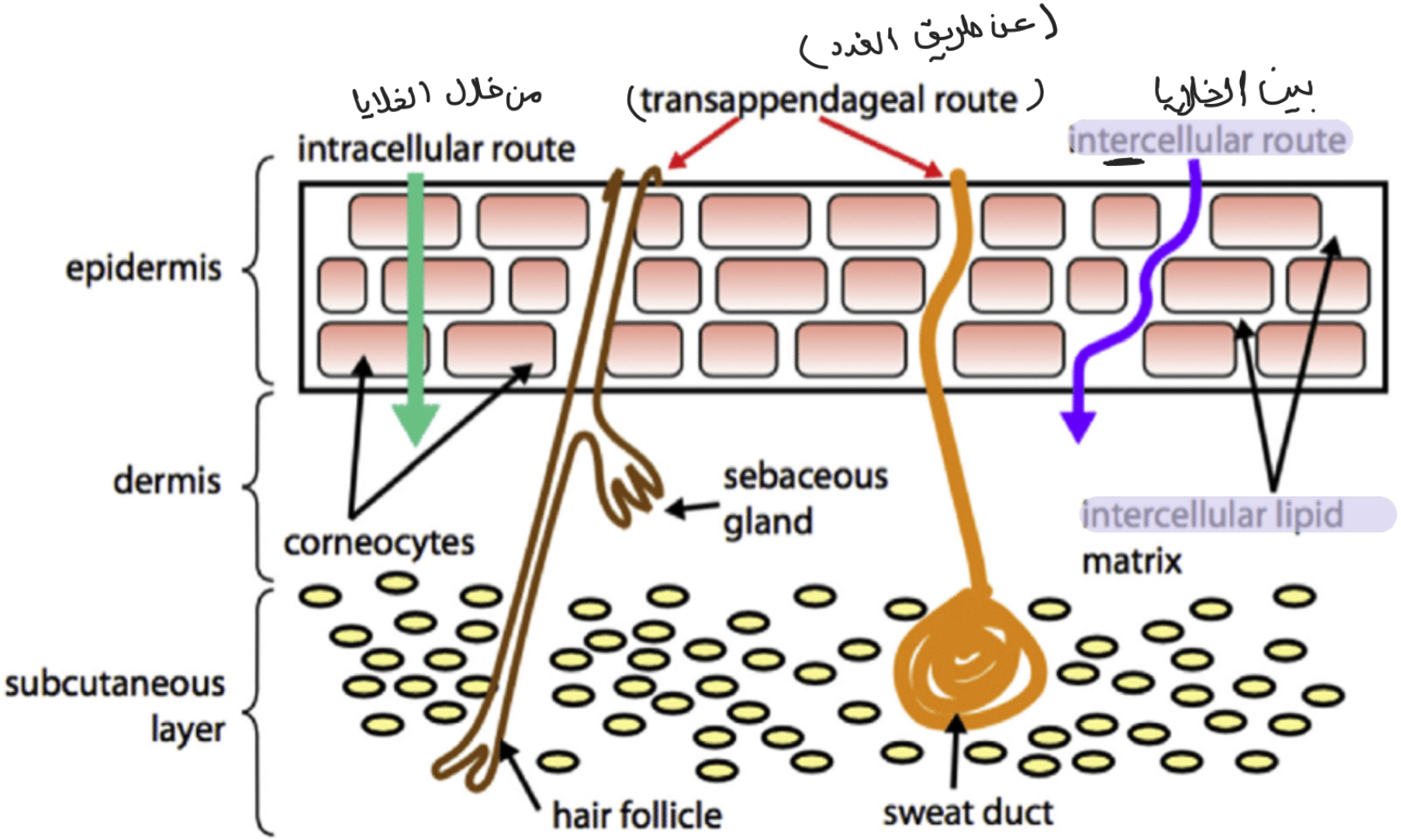
2. Intercellular route:

   allows diffusion of lipophilic or non-polar solutes throught the continuous lipid matrix

B. Trans-appendegeal pathways

   involves the passage of molecules through sweat glands and across the hair follicles

بصيلات الشعر


(عن طريق الغدد)
من خلال الخلايا
(transappendageal route)
بين الخلايا
intracellular route
intercellular route
epidermis
dermis
subcutaneous layer
corneocytes
sebaceous gland
intercellular lipid matrix
hair follicle
sweat duct

Advantages of TDD

- Easy to apply
- Permits self-administration
- Non-invasive (no needles or injections)
- Improves patient compliance
- Reduces first-pass metabolism effect
- Avoid GIT incompatibility (GIT side effect, drug stability and absorption problems)
- Sustains therapeutic drug levels
- Rapid removal in case of toxicity

Disadvantages of TDD

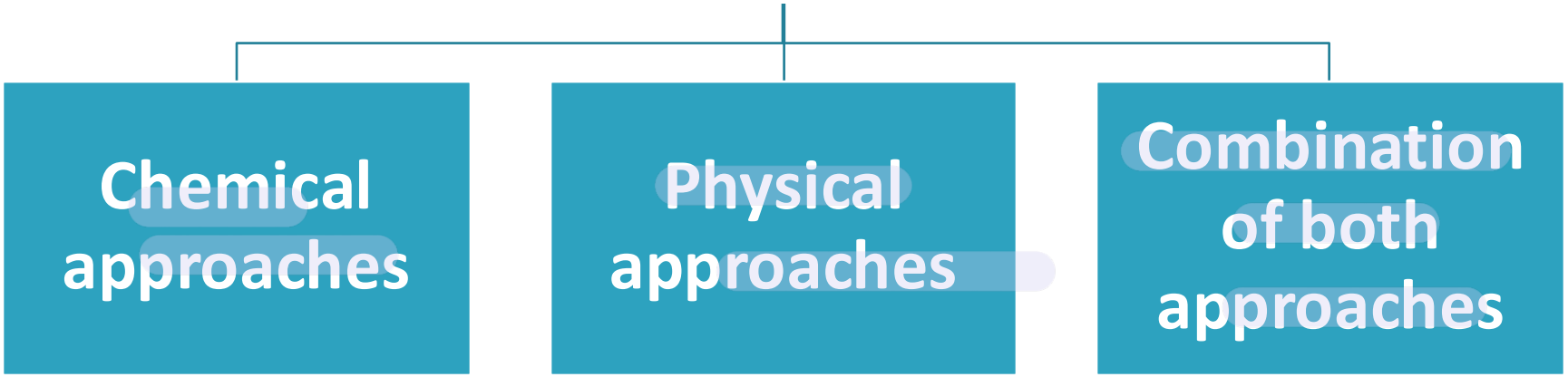
- Local irritation
- Drugs that require high blood levels cannot be administered " limited only to potent drug" → تركيز قليل و بعطيني تأثير كبير
- It is not means to achieve rapid drug action . مفعول يحتاج وقت اطول
- Drugs having very low or high partition coefficient fail to reach systemic circulation
- Drugs having higher molecular weight fail to penetrate the stratum corneum
- Barrier function changes from patient to patient or within the same patient مفعول الدواء رح يختلف من منطقة لمنطقة

Challenge aspect of TDD

- The most challenging aspect of TDD is to overcome the SC barrier, deliver the drug to the skin, and allow the drug to diffuse to reach the blood vessels in the dermis.
- Only a select few drugs, those possessing specific physicochemical properties, are able to pass through the skin into the plasma.
- A drug candidate for transdermal delivery should ideally have a molecular weight of less than 500 Da with a moderate lipophilicity (log P range 1–3) to pass freely through the skin.
- Where as hydrophilic and macromolecular drugs, such as peptides, are frequently hampered by the barrier of the stratum corneum (SC)

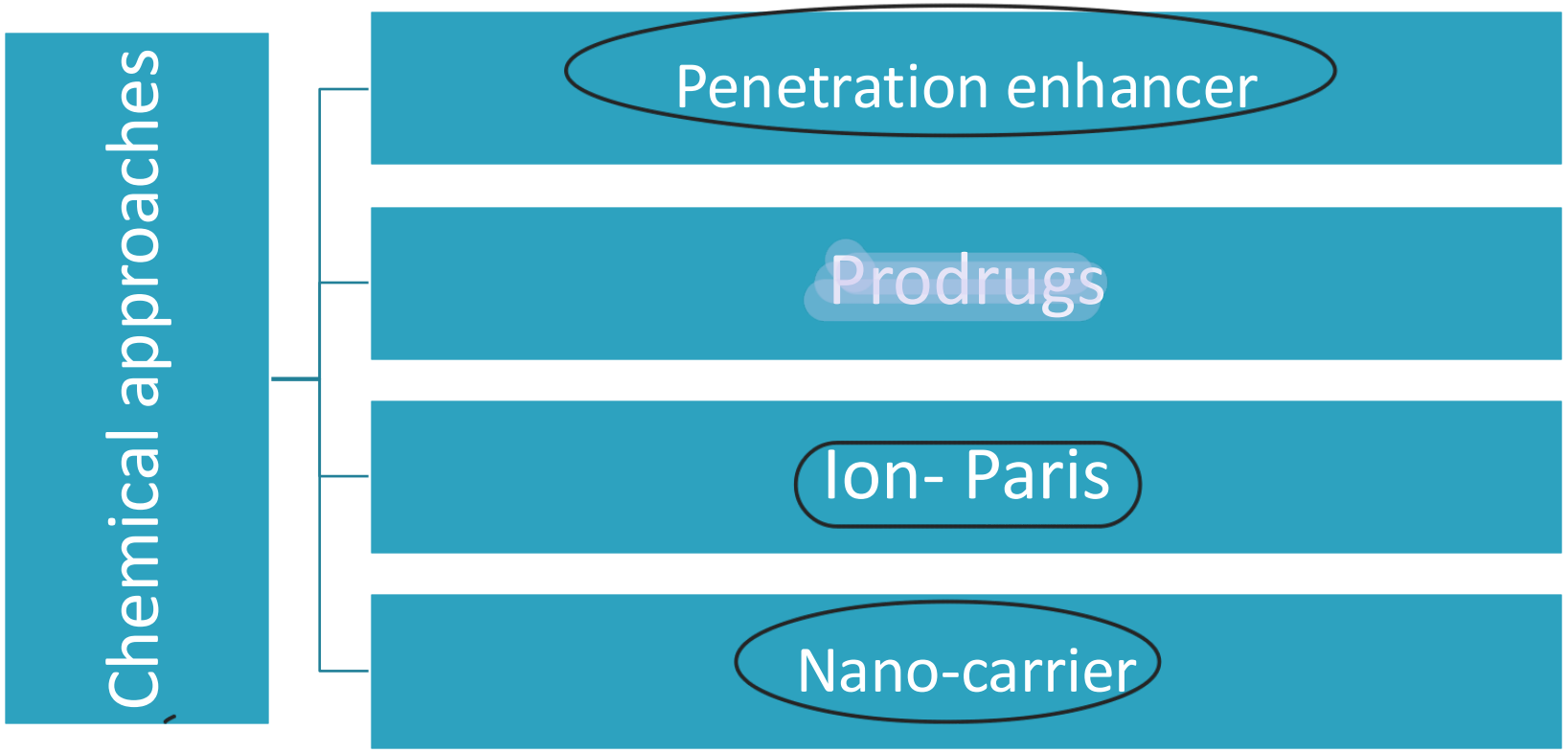
ما يخترقوا

Approaches for enhancing drug transport across the skin



Chemical approaches

- Chemical methods include the influencing of drug and vehicle interactions and optimization of formulation, in order to modify the stratum corneum structure.
- Chemical methods are the most commonly explored approach to transdermal drug permeation enhancement since they are relatively affordable and simple to produce, offer design flexibility, and allow patients to self-administer their drugs.
- Chemical methods are relatively easy to incorporate into creams or gels, as well as skin patches, that can be applied anywhere on the body for short- and long-term systemic administration
- However, the main drawback of chemical methods may be a lag time in drug release incurred with obvious negative influence on rapid onset drugs, such as insulin.

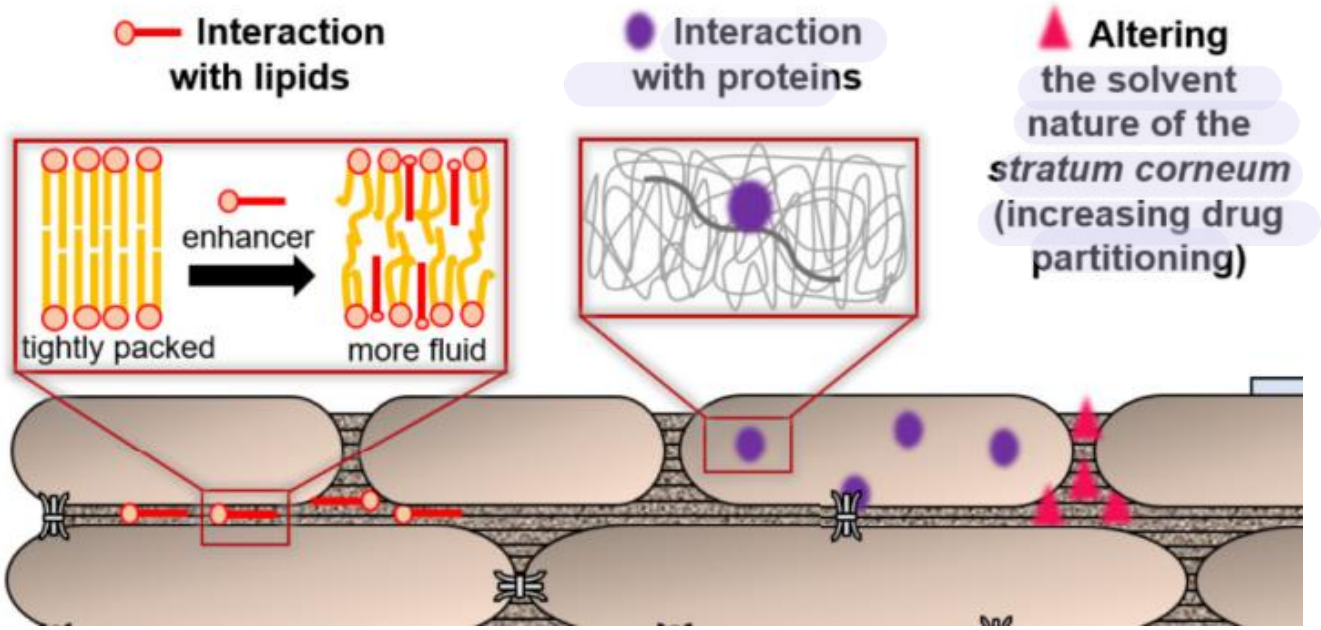

Chemical approaches
Penetration enhancer
Prodrugs
Ion- Paris
Nano-carrier

Chemical Penetration Enhancers (CPEs)

- CPEs are substances that have been examined for their capacity to boost drug molecule transport across the skin.
- They achieve their action through a variety of mechanisms that are dependent on the chemical composition of CPEs, such as:
  1. disrupting the organized lipid bilayer.
  2. interacting with cell membrane proteins
  3. interacting with intercellular proteins
  4. disruption of intercellular lipids
  5. enhancing hydration in the SC
- The optimum enhancer should be nontoxic and bio-compatible and its activity and duration of action should be predictable and consistent at the same time.

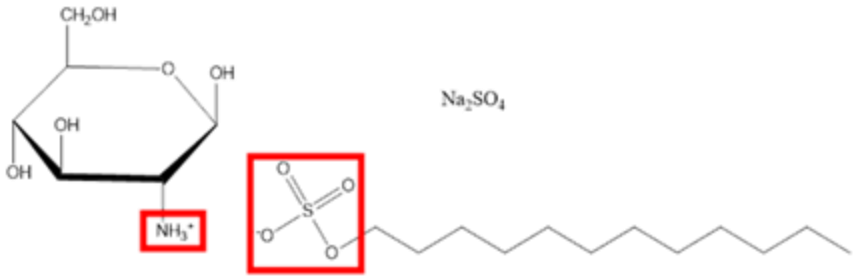
Chemical Penetration Enhancers (CPEs)

- The most frequently used CPEs are alcohols, sulphoxides, azone, pyrrolidones, essential oils, terpenes, fatty acids, and urea.



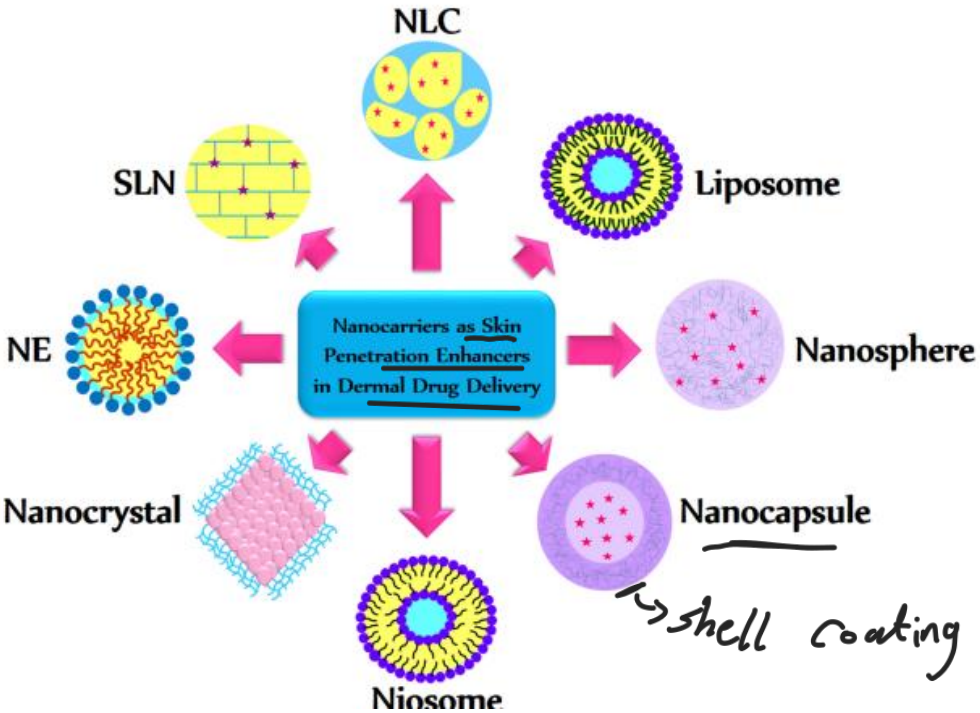
Ion-pairs

- Charged drug molecules don't readily partition into or permeate through human skin.
- Formation of lipophilic ion-pairs increase stratum corneum penetration pf charged species.
- This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralized so that the complex can partition into the stratum corneum
- The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug that can diffuse within the epidermal and dermal tissues

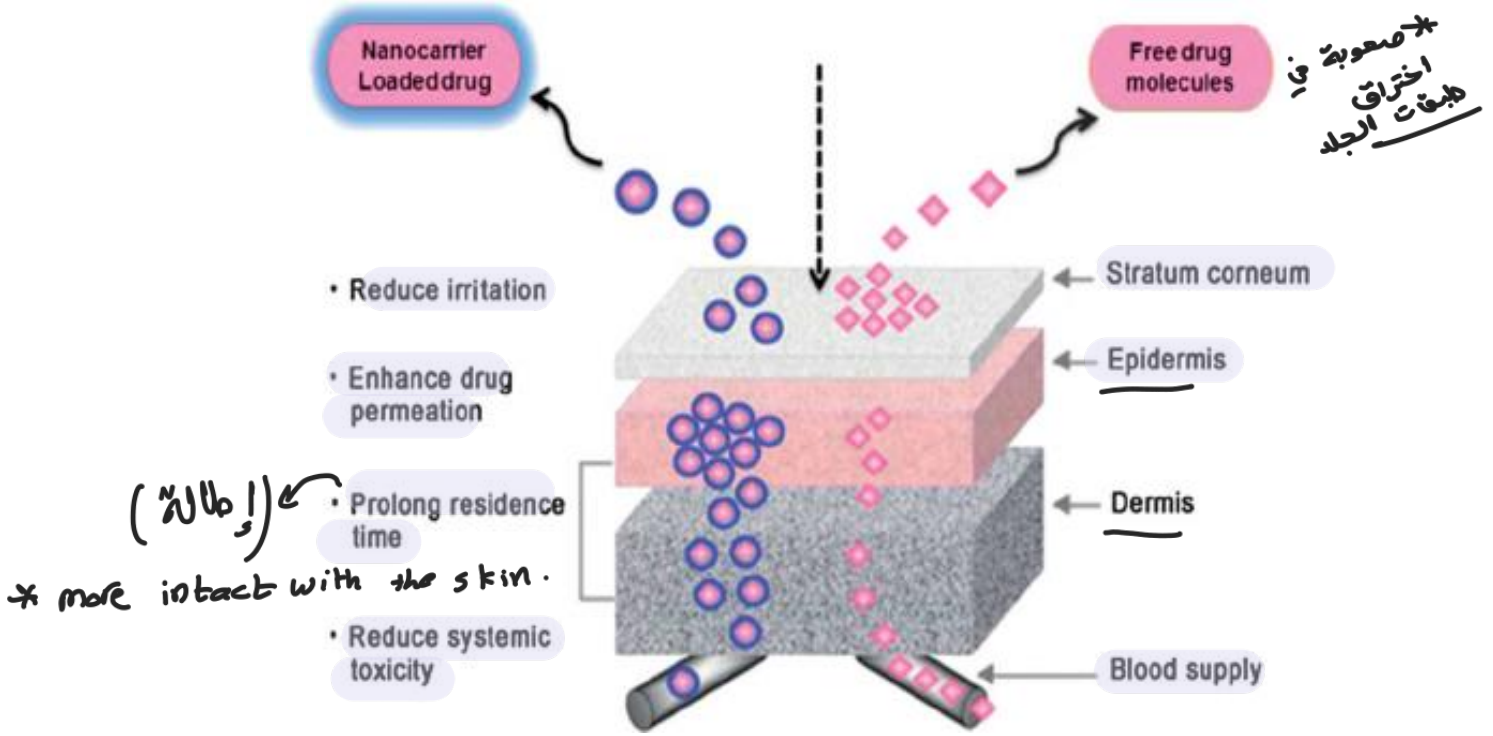


Nanocarriers

- Nanocarriers are defined as colloidal systems with an average diameter of fewer than 500 nanometers.
- Novel nanocarriers such as microemulsion, nanoemulsion, liposome, and nanoparticulate carriers were most investigated with the purpose of dermal and transdermal drug delivery.



- The characteristics of the nano-carrier, rather than the physicochemical properties of drug molecules, control the clearance and tissue distribution profile of a drug when delivered by such a delivery system

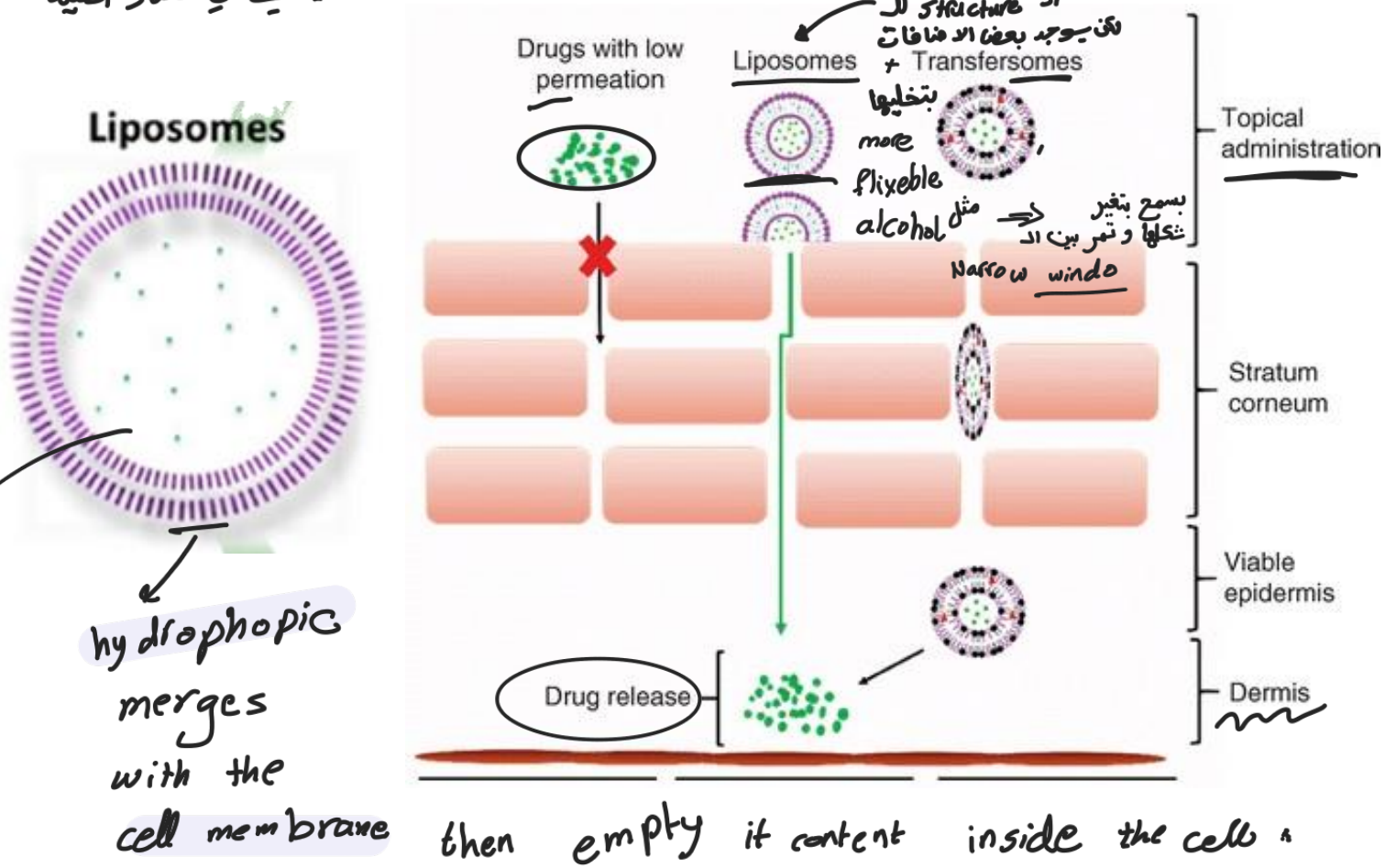


حويصلي

- Liposomes are vesicular systems with an aqueous internal environment made up of phospholipids and fatty acids that are essentially biocompatible and biodegradable due to their natural abundance In cell membranes.

تواجدهم بشكل طبيعي في غشاء الخلية

قابلة للتحلل البيولوجي



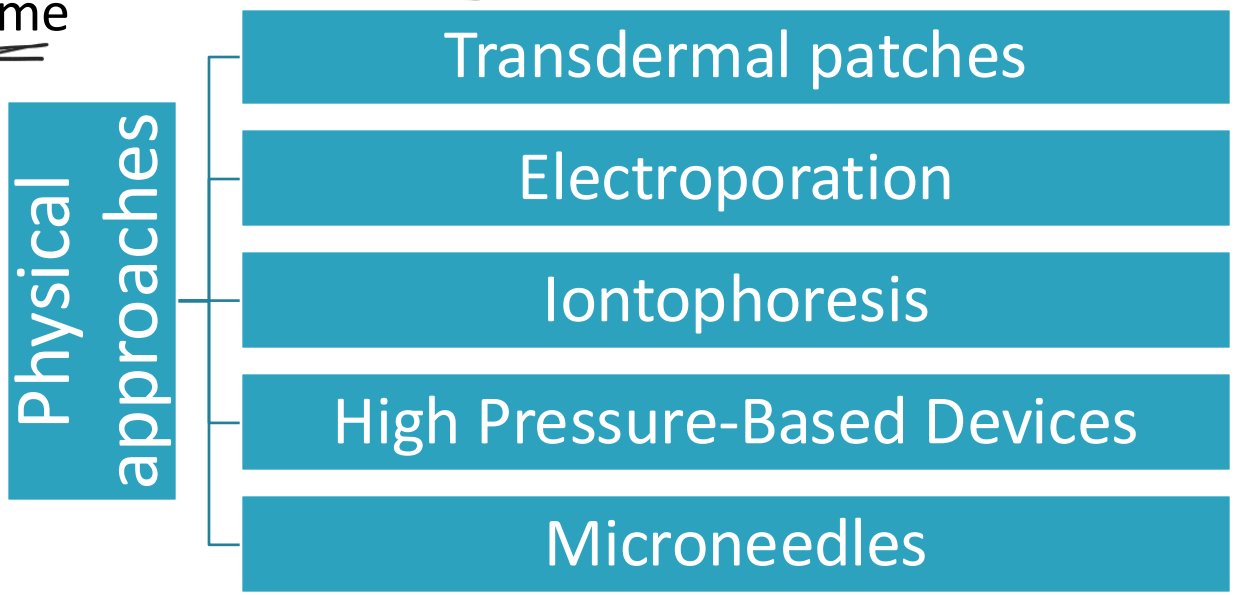
Physical approaches

- To increase drug transport via the skin, physical techniques utilize external energy as a driving force or physically disrupt the SC.

بستخدم هذه الفاهيك في هذه الطرق ٥-

- Many drugs, including lipophilic and hydrophilic molecules, vaccines, and macromolecules, can be delivered.
- In comparison with chemical approaches, this method provides more control over drug delivery patterns, resulting in a shorter lag time

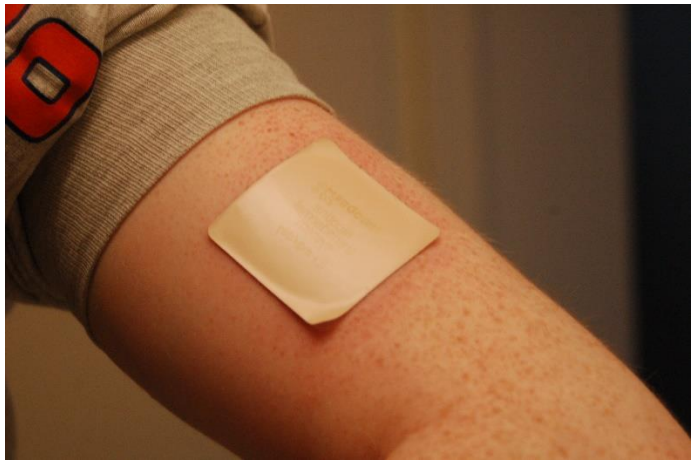
مباشرة بوصل للدم



Transdermal patches

- A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. → مجرى الدم
- Advantages of skin patch:
  - Easy to apply and to remove
  - Avoids liver" first pass effect"
  - Improve patient compliance

تحسن التزام المرضى بأخذه



- Disadvantages of skin patch:
  - Can irritate skin
  - Adhesive bond may fail ممكن يصيرلها removal
  - Sometimes slow to take an effect

بعض الأنواع بتكون (Long Lag time)

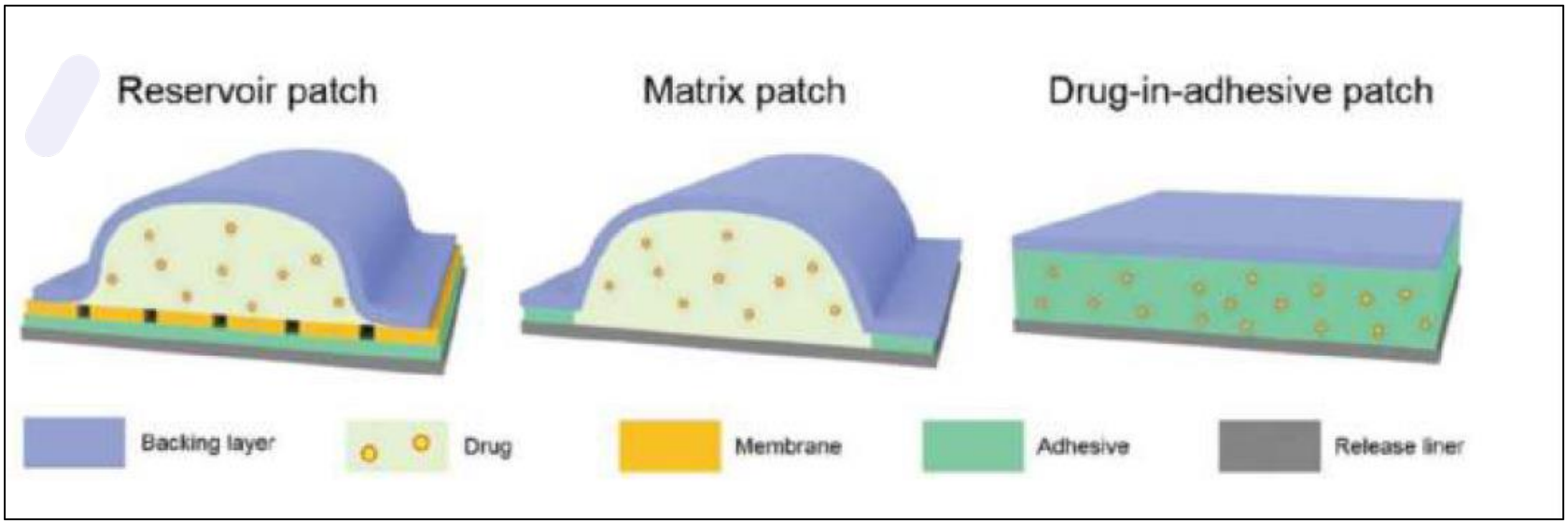
Components of transdermal patch

- Liner : protects the patch during storage. The liner should be removed before it s use.
- Drug
- Adhesive: it serves to adhere the components of the patch together along with adhering the patch to the skin. E.g. Acylic polyisobutylene (PIB), and silicone.
- Membrane: it controls the release of the drug from the reservoir and multi-layer patches.
- Backing: the film protects the patch from the outer environment.

Transdermal patches

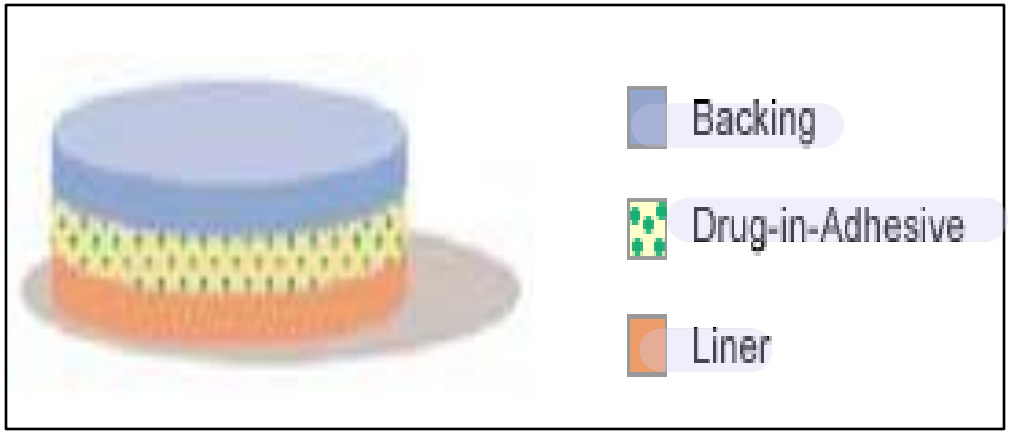
There are four main types of transdermal patch

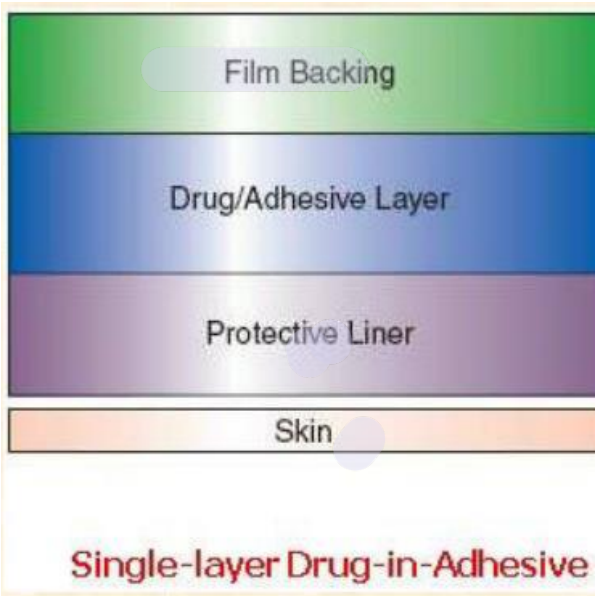
1) Single-layer Drug-in-Adhesive
2) Multi-layer Drug-in-Adhesive
3) Drug Reservoir-in-Adhesive
4) Drug Matrix-in-Adhesive



1) Single-layer Drug-in-Adhesive

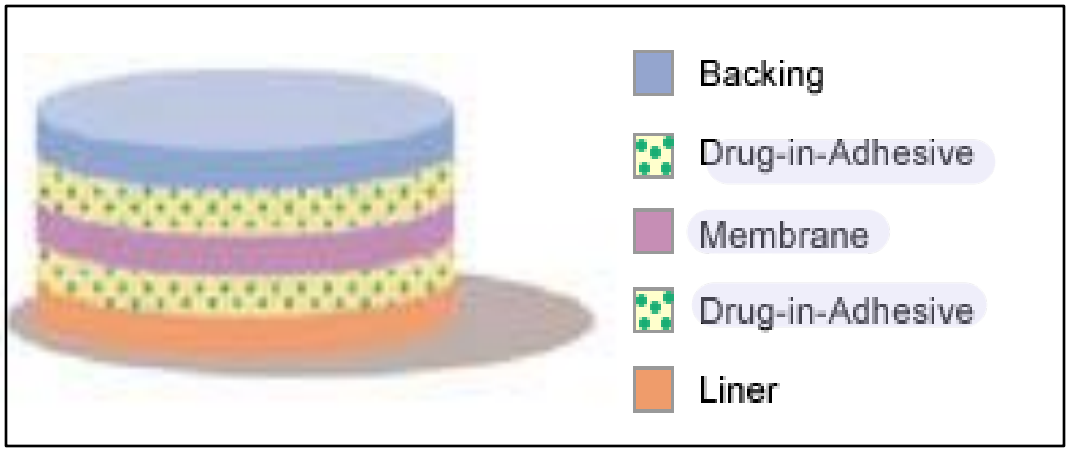
- The adhesive layer of this system also contain the drug.
- In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug.
- The adhesive layer is surrounded by a temporary linear and backing.

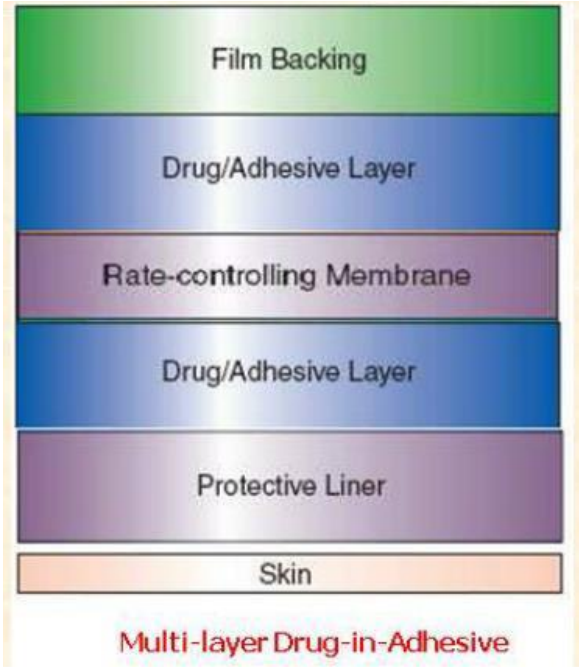




2) Multi-layer Drug-in-Adhesive

- Is similar to the single-layer system in that adhesive layers are also responsible for the releasing of the drug.
- One of the layers is for immediate release of the drug and other is for control release of drug from the reviser.
- The multi-layer system is different however that it adds another layer of drug in adhesive, usually separated by a membrane.





For both drug- in- adhesive type of patch:

- The release rate controlling factors include:

  Thickness of adhesive layer

- Polymers:

  cross-linked gelatin or lecithin

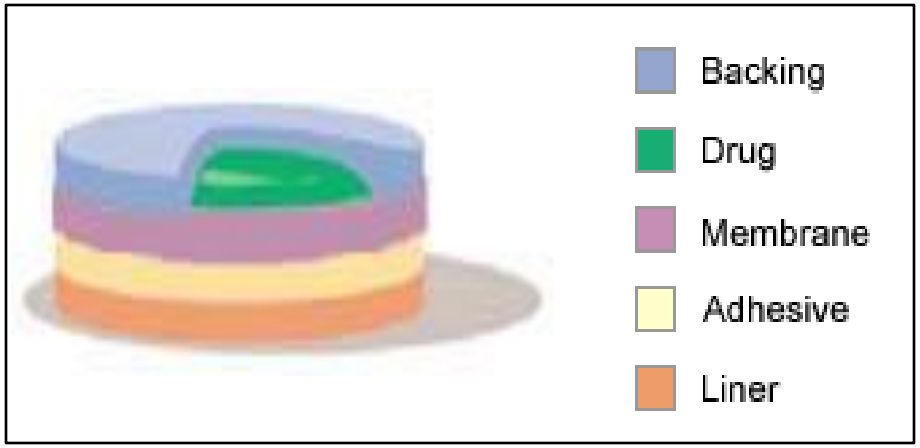
- Advantages:

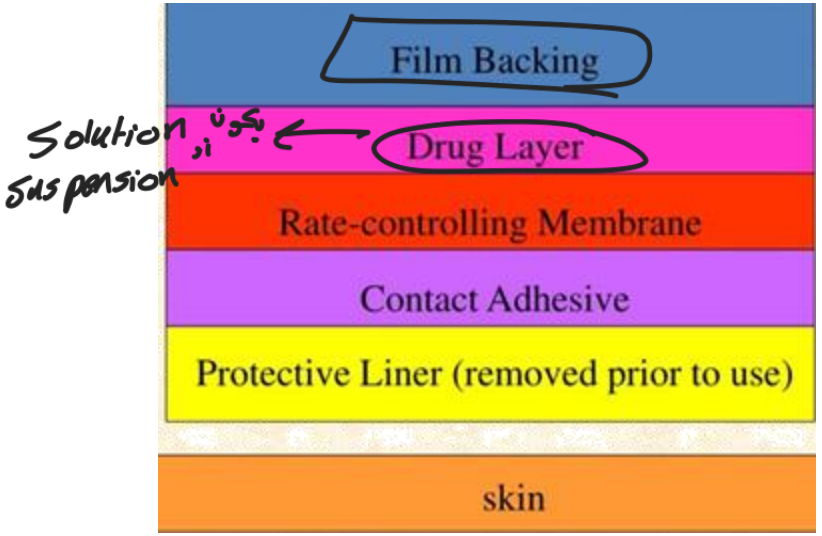
  A system in which the drug is incorporated directly into the adhesive, rather than into a separated layer, usually used for smaller weight compounds.

الدواء بكون متصل بشكل مباشر مع الـ skin

3) Drug Reservoir-in-Adhesive

- The Reservoir transdermal system design is characterized by the inclusion of a liquid compartment containing a drug solution or suspension separated from the release liner by a semi-permeable membrane and adhesive.





خزان في مادة لاصقة .

3) Drug Reservoir-in-Adhesive

- The release rate controlling factors include:

Membrane thickness

- Polymers:

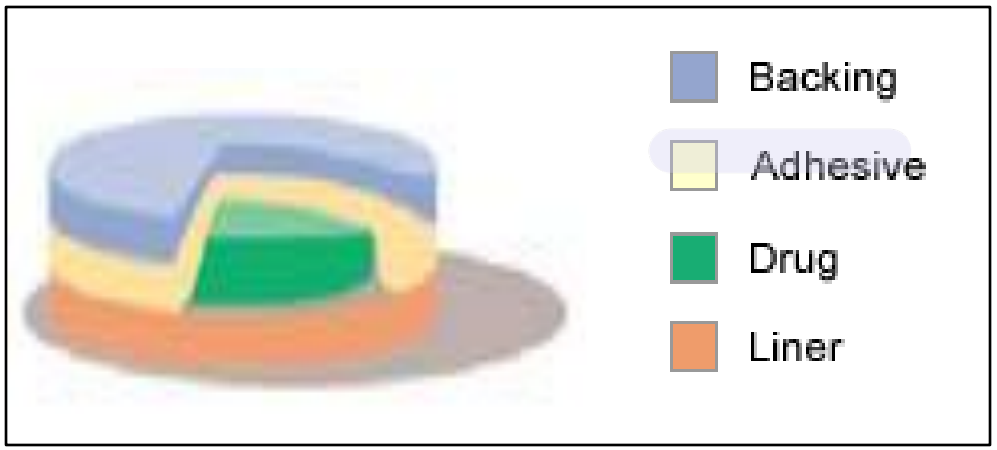
Cellulosic esters, polyamids or PVC

- Advantages:

Used when drug require significant penetration enhancement and/or high dosage level.

4) Drug Matrix-in-Adhesive

- The Matrix system design is characterized by the inclusion of a semisolid matrix containing a drug solution or suspension which is in direct contact with the release liner.
- The component responsible for skin adhesion is incorporated in an overlay and forms a concentric configuration around the semisolid matrix.



4) Drug Matrix-in-Adhesive

- The release rate controlling factors include:

* Drug concentration in polymer matrix
* Chemical nature of polymer matrix
* Geometry of device

- Polymers:

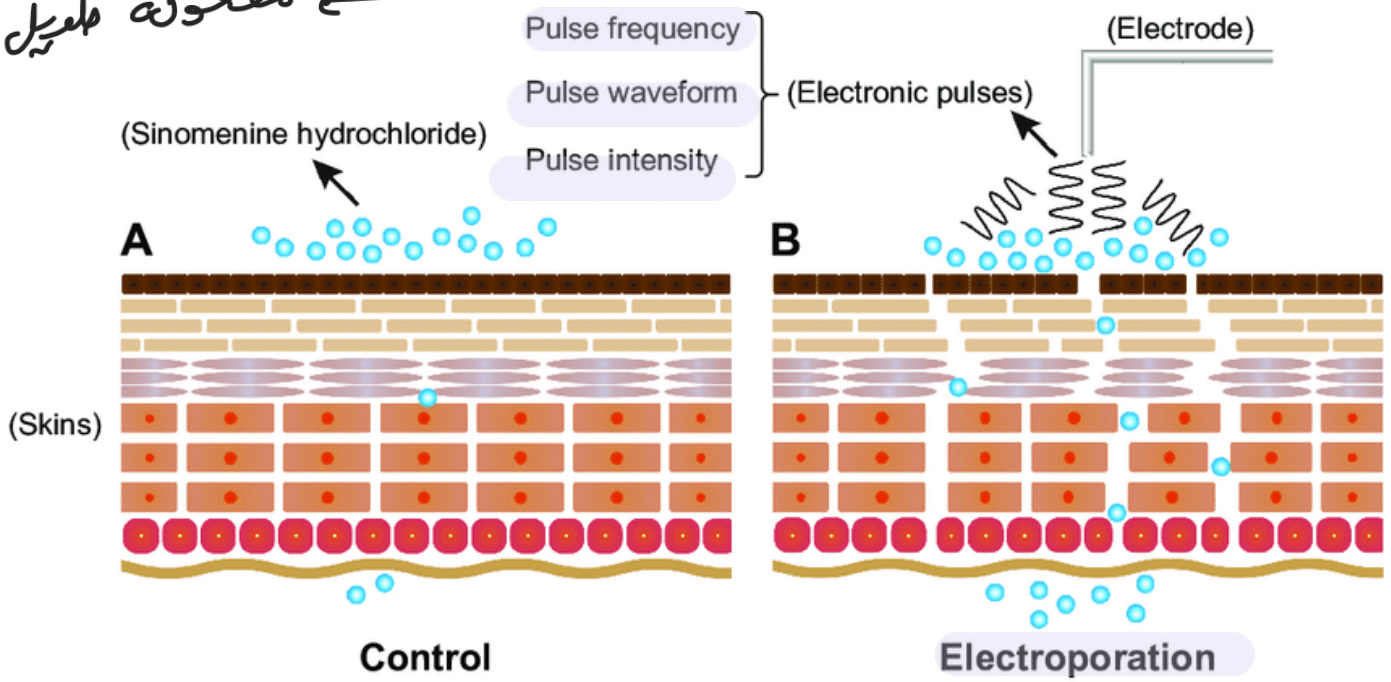
PVP, Ethylene vinylacetate, polypropylene.

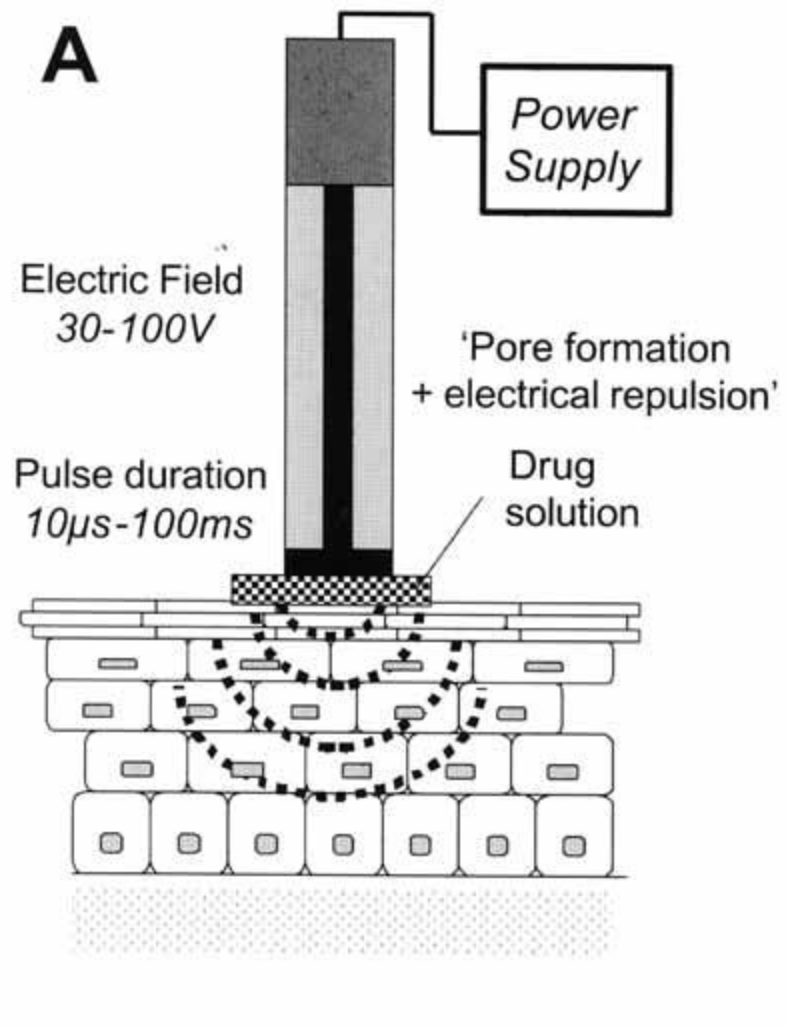
- Advantages:

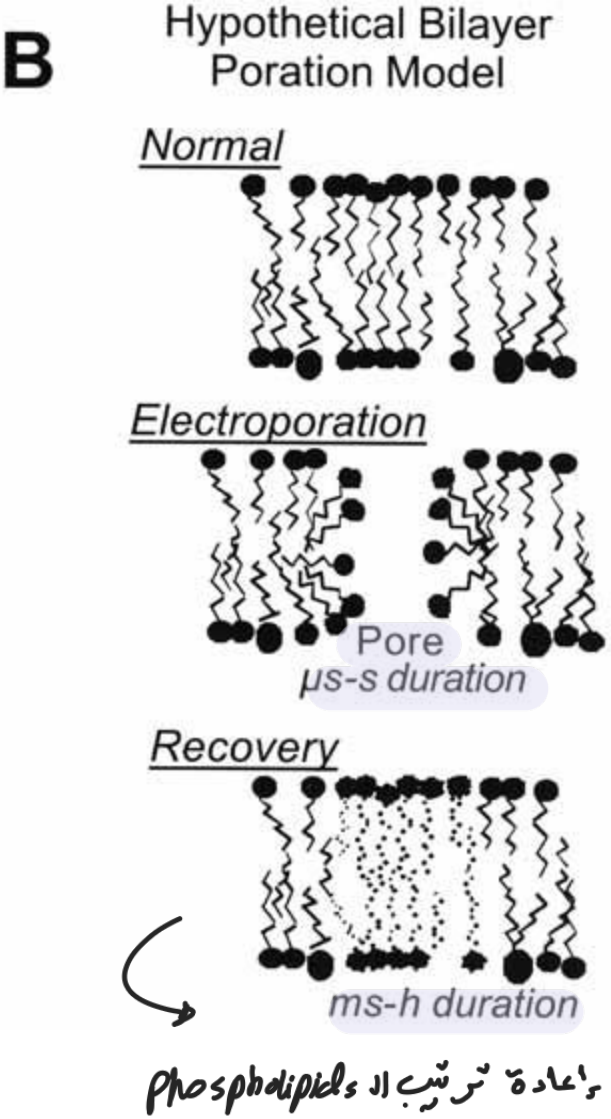
* Sleeker and thinner
* Daily or multiple –day applications
* Appropriate for drugs that penetrate readily and/ or have low dosage reguirments.

Electroporation

- Applying high intensities of electric pulses on skin cells leads to the formation of aqueous pores and other structural rearrangements in the lipid membranes of the SC, allowing the diffusion of drugs across the skin.
- The electric pulses applied for milliseconds allow the diffusion of drugs through long-lived electropores for up to several hours.







واعادة ترتيب الـ phospholipids

Electroporation

عدم معرفة كمية الدواء اللي وصلت للـ Blood

١

- The main drawbacks are the lack of quantitative delivery, cell death with high fields and potential damage to labile drugs, e.g., those of protein origin.

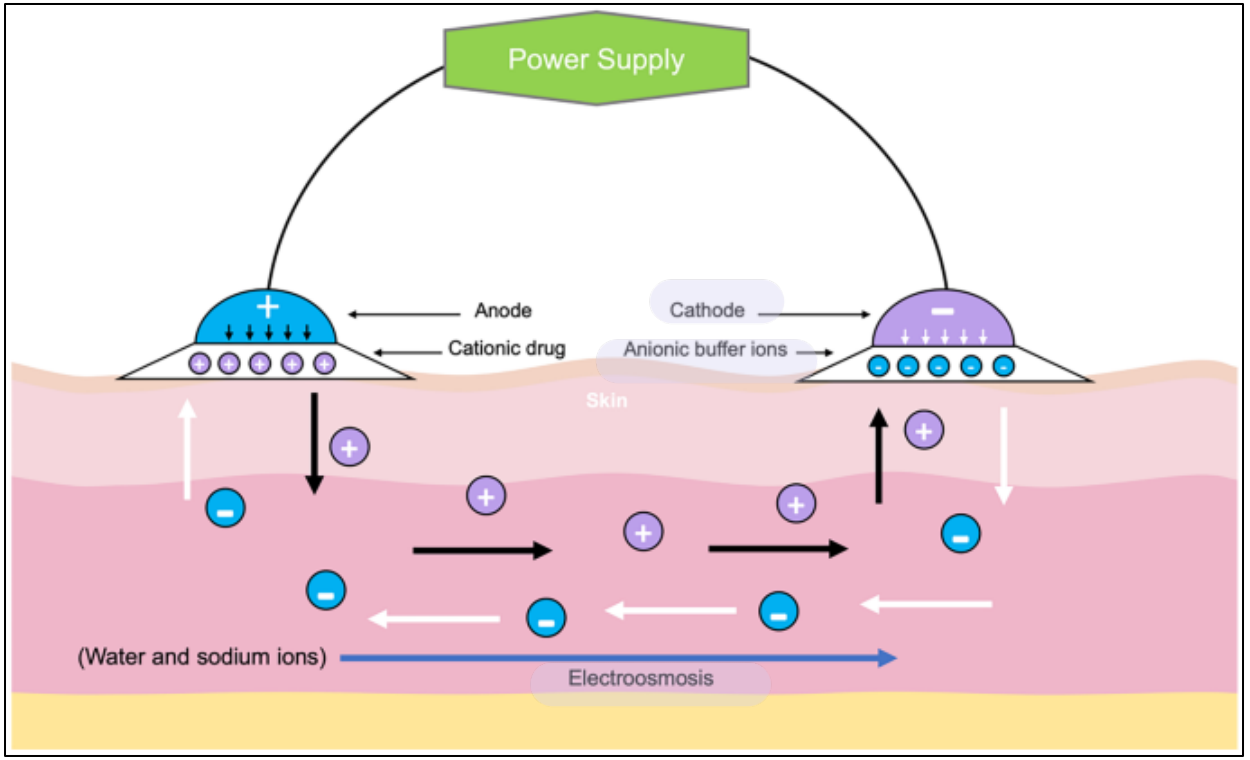
مثال

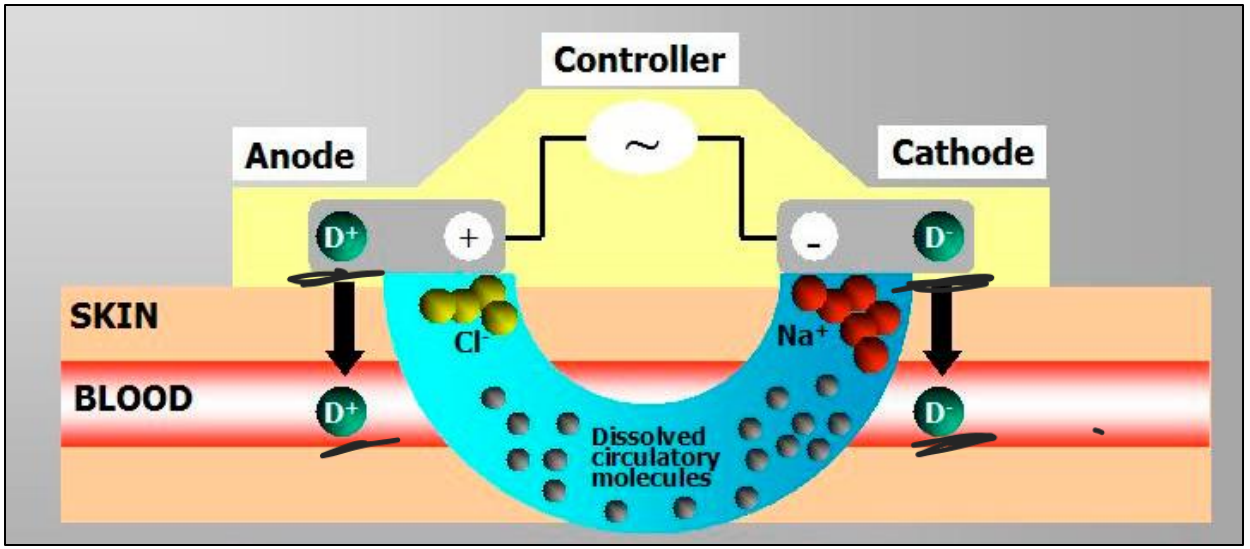
غير مستقر

(physical approach)

Iontophoresis

- Iontophoresis involves the application of physiologically acceptable electrical currents (0.1–1.0 mA/cm2) to drive charged permeants into the skin through electrostatic effects and make ionic drugs pass through the skin into the body by its potential gradient.
- While delivering a negatively charged drug across skin, it is placed between the negative electrode and the skin. The ion is then attracted thought the skin towards the positive electrode.
- In case of positively charged drug, it is placed between the positive electrode and skin.


Power Supply
Anode
Cationic drug
Cathode
Anionic buffer ions
Skin
(Water and sodium ions)
Electroosmosis


Controller
Anode
Cathode
D+
+
-
D-
SKIN
BLOOD
Cl-
Na+
D+
D-
Dissolved
circulatory
molecules

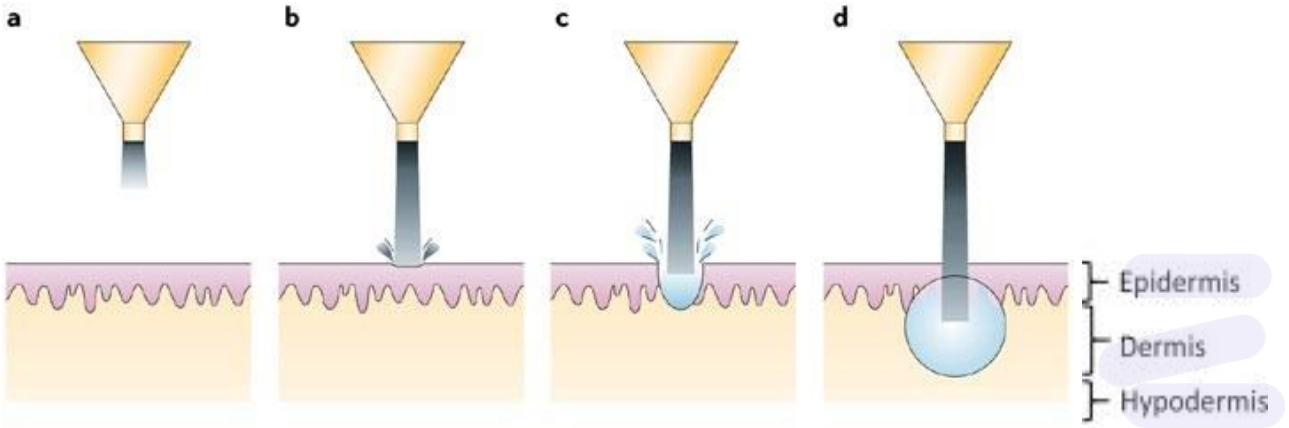
- Proteins and peptides are considered ideal candidates for iontophoresis as they are usually charged at physiological pH or can have their charges altered by altering pH.
- Although iontophoresis does appear to offer numerous advantages, there are still concerns about its safety which are intimately linked to the efficiency of iontophoresis devices.
- Furthermore, iontophoresis devices are generally expensive and quite complex, rendering (يقدم) them a less favorable approach from the perspective of patient compliance.
- Moreover, the corrosion of the metal components (تآكل) of electrodes upon storage remains an issue.

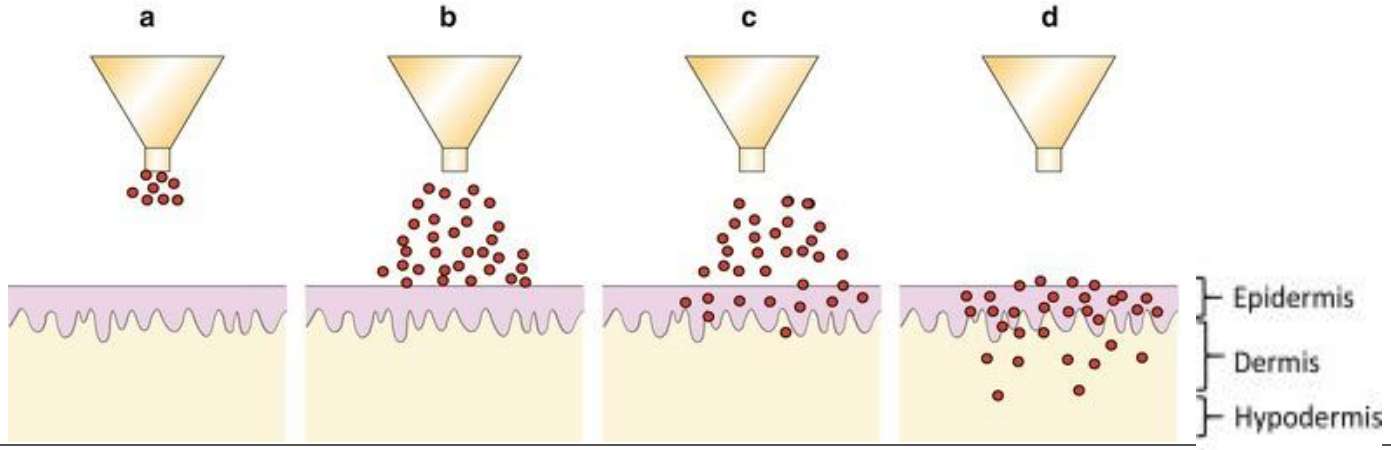
High Pressure-Based Devices

- High pressure based devices is an attractive alternative to needle-based injection, the needle-free jet injector is a device that generates high-speed (120–200 m/s) jets of either powder or liquid jet injections that puncture the skin and deliver drugs using a power source such as compressed gas or a spring.
- Although jet injections rupture the epidermal layer, which is reversible in nature , this technique is known to be:
- Painless
- Noninvasive.
- Greater patient compliance, especially in chronic disease cases,
- Minimization of infections and disease transmissions that result from improper reuse of needles.
- As the delivery of drugs via jet injection is not dependent on their diffusion rates, this method overcomes the limits of existing drug delivery technologies, such as iontophoresis and electroporation

ما في Drug لل Diffusion

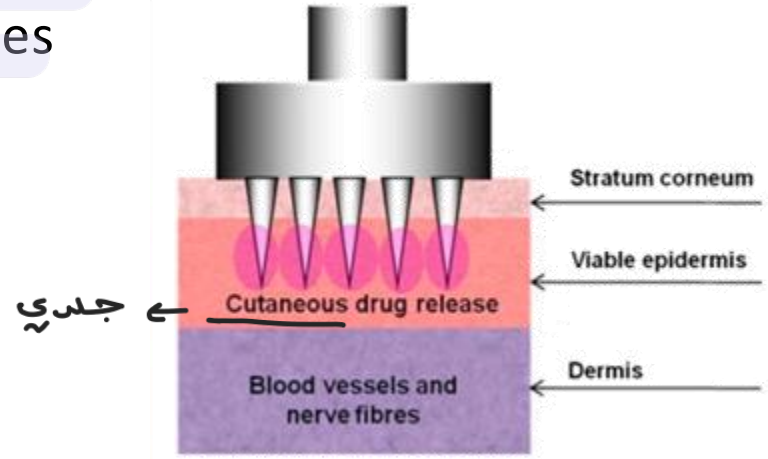
بهاي الحالة -

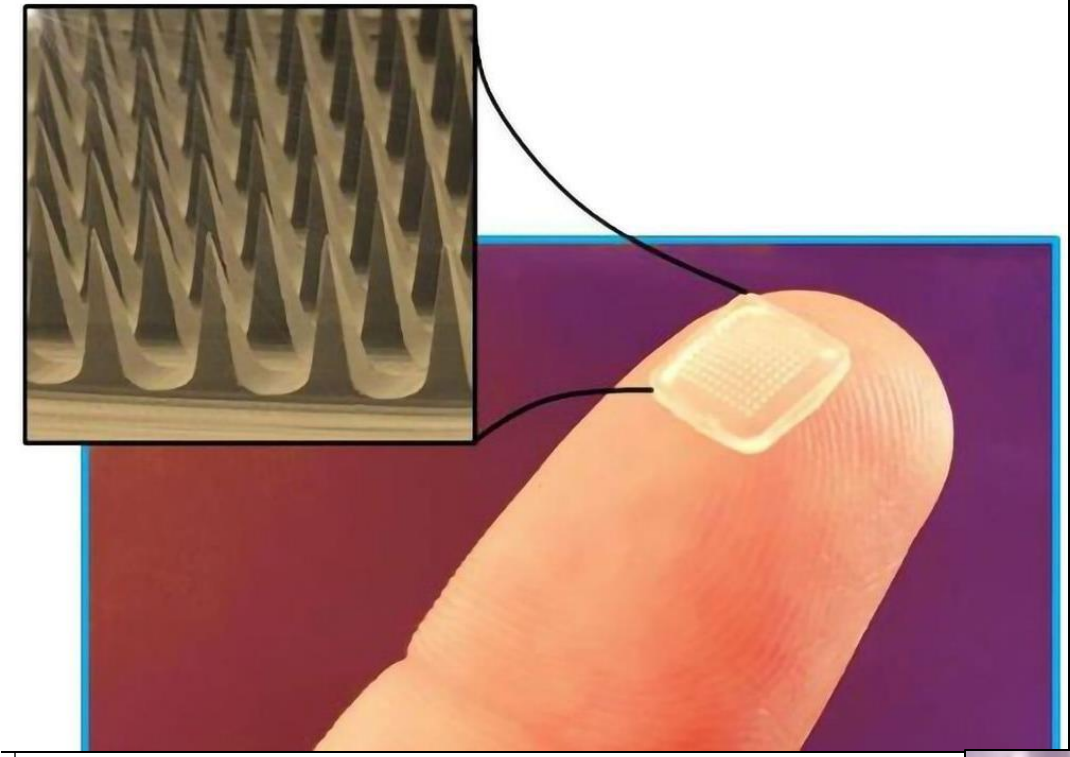




Microneedles

- Microneedles (MNs) are microscopic projections that disrupt the top layer of the skin in a non-invasive manner, creating micron-sized channels ranging in height from 25 to 2000 m that allow drugs to reach the epidermis or upper dermis directly.
- (MNs) have received a lot of interest because of their painlessness and ease of usage for patients .
- MNs have facilitated the transdermal delivery of not only low-molecular weight drugs but also hydrophilic molecules, peptides and proteins, cosmeceuticals, microparticles, vaccines, and nanoparticles





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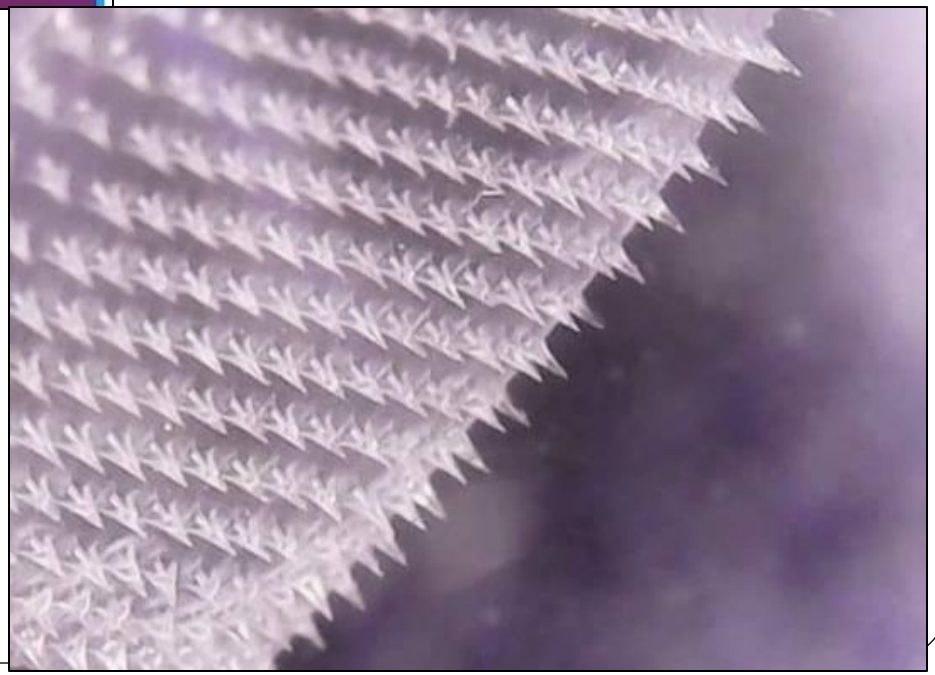
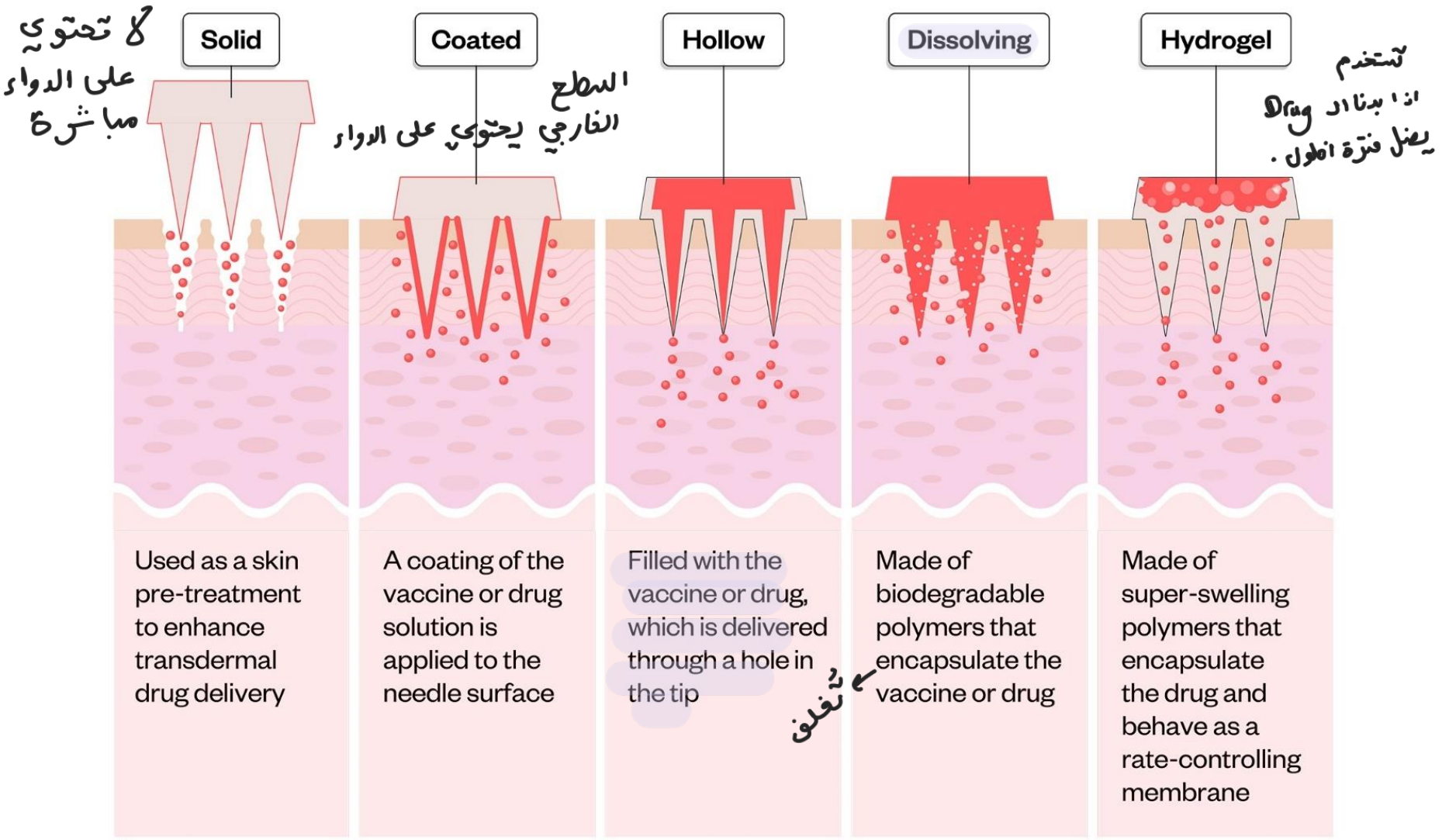
hydrogel



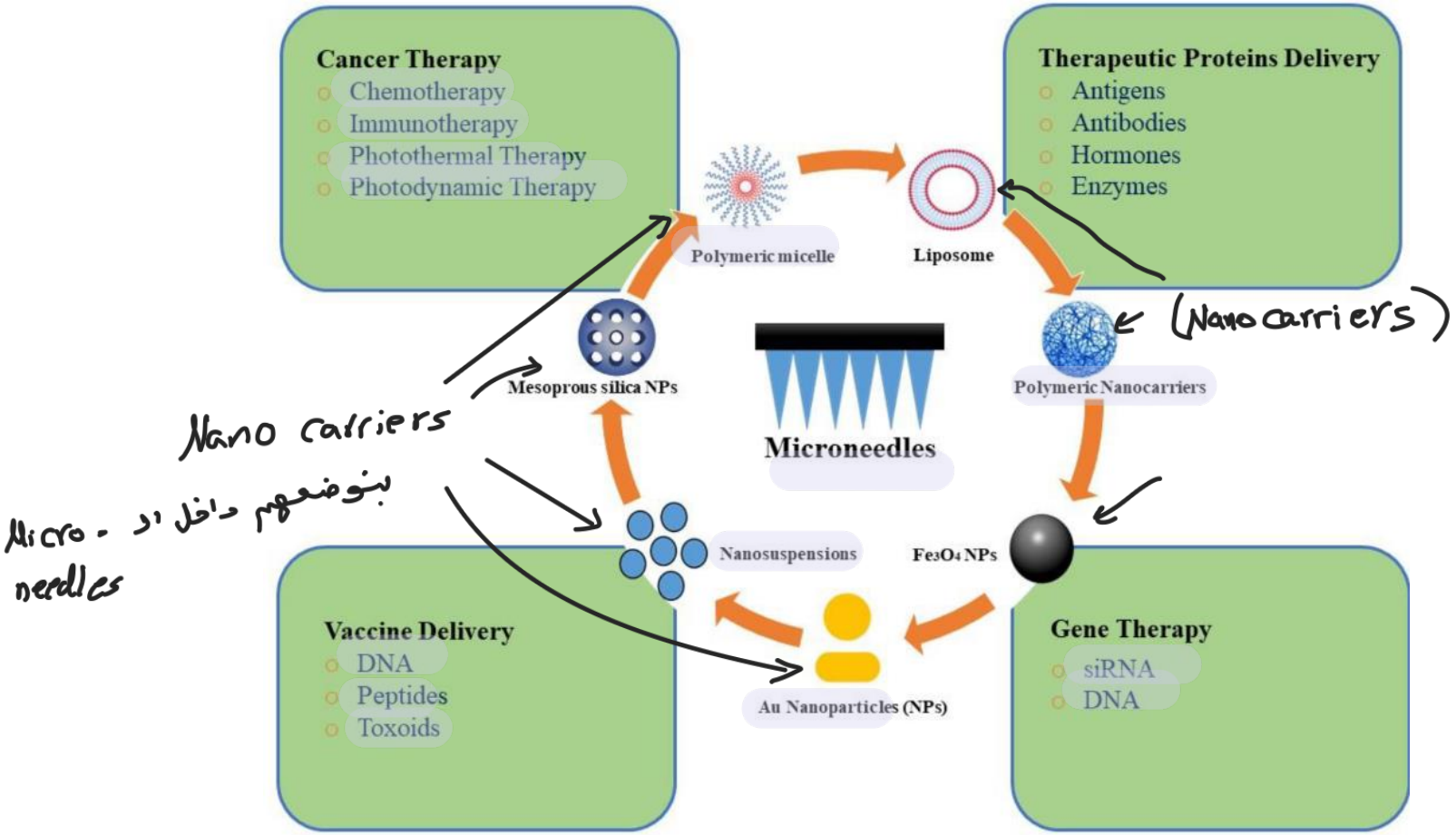
MN application methods



Integrating physical with chemical technologies

- Physical techniques have been exploited as a unique TDD platform for successful drug penetration in the treatment of a variety of disorders.
- However, difficulties such as hydrophobic drug-loading capacity limitations, stability issues, and unpredictable drug-release rates, limit the use of physical methods.
- Drawing inspiration from the ways in which nanomedicine combined with physical approaches created new paths for disease therapy, the use of nanomedicine, in particular, can alleviate a number of issues associated with drugs, including poor solubility, poor stability, low bioavailability, and nonspecific distribution throughout the body.
- Therefore, integrating physical with chemical technologies is a huge step forward from conventional TDDs.

- Microparticles and nanoparticles are being used in a new generation of MNs to help achieve long-acting benefit after delivery into the body



Thank you

MSc. Mai Jaber